



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/165, 31/215, 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54</b>		A1	(11) International Publication Number: <b>WO 98/17267</b> (43) International Publication Date: 30 April 1998 (30.04.98)																																
(21) International Application Number: <b>PCT/US97/18864</b> (22) International Filing Date: 23 October 1997 (23.10.97)  (30) Priority Data: <table><tr><td>08/736,318</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/735,873</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/735,881</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/736,222</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/736,221</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/735,870</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/735,876</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/736,220</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/736,319</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/735,874</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr><tr><td>08/736,228</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr></table>		08/736,318	23 October 1996 (23.10.96)	US	08/735,873	23 October 1996 (23.10.96)	US	08/735,881	23 October 1996 (23.10.96)	US	08/736,222	23 October 1996 (23.10.96)	US	08/736,221	23 October 1996 (23.10.96)	US	08/735,870	23 October 1996 (23.10.96)	US	08/735,876	23 October 1996 (23.10.96)	US	08/736,220	23 October 1996 (23.10.96)	US	08/736,319	23 October 1996 (23.10.96)	US	08/735,874	23 October 1996 (23.10.96)	US	08/736,228	23 October 1996 (23.10.96)	US	(72) Inventors; and (75) Inventors/Applicants (for US only): <b>ORME, Mark, W. [US/US]; 636 N.W. 98th Street, Seattle, WA 98117 (US). BAINDUR, Nand [IN/US]; 13919 57th Place West, Edmonds, WA 98026 (US). ROBBINS, Kirk, G. [US/US]; 1200 Grant Avenue South #Y-304, Renton, WA 98055 (US). HARRIS, Scott, M. [US/US]; 6825 31st Avenue N.E., Seattle, WA 98815 (US). KONTOYIANNI, Maria [GR/US]; 769 Hayes Street #504, Seattle, WA 98109 (US). HURLEY, Laurence, H. [US/US]; 5915 Northwest Place, Austin, TX 78731 (US). KERWIN, Sean, M. [US/US]; 703 Ivy Court, Round Rock, TX 78681 (US). MUNDY, Gregory, R. [US/US]; 3719 Morgan's Creek, San Antonio, TX 78230 (US). PETRIE, Charles [US/US]; 18459 N.E. 196th Place, Woodinville, WA 98072 (US).</b>
08/736,318	23 October 1996 (23.10.96)	US																																	
08/735,873	23 October 1996 (23.10.96)	US																																	
08/735,881	23 October 1996 (23.10.96)	US																																	
08/736,222	23 October 1996 (23.10.96)	US																																	
08/736,221	23 October 1996 (23.10.96)	US																																	
08/735,870	23 October 1996 (23.10.96)	US																																	
08/735,876	23 October 1996 (23.10.96)	US																																	
08/736,220	23 October 1996 (23.10.96)	US																																	
08/736,319	23 October 1996 (23.10.96)	US																																	
08/735,874	23 October 1996 (23.10.96)	US																																	
08/736,228	23 October 1996 (23.10.96)	US																																	
(71) Applicants (for all designated States except US): <b>ZYMOGENETICS, INC. [US/US]; 1201 Eastlake Avenue East, Seattle, WA 98102 (US). OSTEOSCREEN, INC. [US/US]; Suite 201, 2040 Babcock Road, San Antonio, TX 78229 (US). UNIVERSITY OF TEXAS AUSTIN [US/US]; 201 W. 7th Street, Austin, TX 78701 (US).</b>		(74) Agents: <b>MURASHIGE, Kate, H. et al.; Morrison &amp; Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).</b>																																	
		(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).																																	
<p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>																																			
(54) Title: COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS																																			
(57) Abstract																																			
Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond <i>per se</i> so as to space the aromatic systems at a distance 1.5-15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.																																			

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

## COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

### Technical Field

5        The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high  
10      throughput screening assay.

### Background Art

Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and  
15      osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. *Clin Orthop* 324:24-28, 1996; Mundy, G.R. *J Bone Miner Res* 8:S505-10, 1993).

20       Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine  
25      bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor  $\beta$ , the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like  
30      growth factor I and insulin-like growth factor II), and a recently described family of

proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor  $\beta$  superfamily. They were first identified by Wozney J. *et al. Science* (1988) 242:1528-5 34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. *Science* (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. *Molec Reprod Dev* (1992) 32:160-67). These factors are expressed by normal osteoblasts as they 10 differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation *in vitro* as well as bone formation *in vivo* (Harris S. *et al. J. Bone Miner Res* (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As 15 osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. *et al. Curr Opin Cell Biol* (1990) 2:1018-27; Harris S. *et al.* (1994), *supra*). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, 20 and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. *et al.* (1994), *supra*). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. *et al.* (1994), *supra*). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are 25 expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation *in vitro* and *in vivo*, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific 30 temporal and spatial patterns. This suggests that BMPs may have effects on many

tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

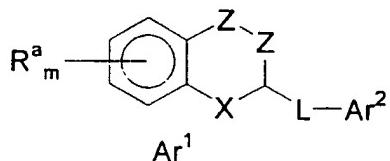
5 There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental  
10 defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by  
15 the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

There are currently no satisfactory pharmaceutical approaches to managing any  
20 of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

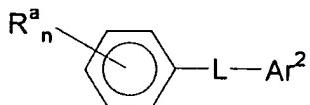
US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl  
25 chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described 5 below and are useful in treating bone disorders. These compounds, generically, are of the formulae



wherein R<sup>a</sup> is a non-interfering substituent;  
10 m is an integer of 0-4;  
each dotted line represents an optional π-bond;  
each Z is independently N, NR, O, S, CR or CR<sub>2</sub>, where each R is  
independently H or alkyl (1-6C);  
X is O, S, SO or SO<sub>2</sub>;  
15 L is a flexible linker; and  
Ar<sup>2</sup> is a substituted or unsubstituted 6-membered aromatic ring; or:



wherein R<sup>a</sup> is a non-interfering substituent;  
n is an integer of 0 and 5;  
20 L is a flexible linker which does not contain nitrogen or is a constrained linker;  
and  
Ar<sup>2</sup> is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the 25 effects of abnormalities in bone formation or resorption. The present invention

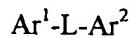
expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

5    Disclosure of the Invention

The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the  
10 invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

15    Therefore, the compounds useful in the invention can be described as having the formula Ar<sup>1</sup>-linker-Ar<sup>2</sup>, wherein each of Ar<sup>1</sup> and Ar<sup>2</sup> is independently an aromatic system and the linker portion of the formula spaces Ar<sup>1</sup> and Ar<sup>2</sup> apart by a distance of approximately 1.5-15 Angstroms. Ar<sup>1</sup>, Ar<sup>2</sup> and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is  
20 preferably at least one nitrogen atom in either Ar<sup>1</sup>, Ar<sup>2</sup> and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

Thus, in one aspect, the invention is directed to a method to treat a condition in  
25 a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:



wherein each of Ar<sup>1</sup> and Ar<sup>2</sup> is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

5 L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

10 Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

15 Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

20 Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

25 Figure 9 shows the results in an *ex vivo* calvarial assay for various compounds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX *in vivo* assay.

30 Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

Figure 12 presents graphs showing results of qCT and bone histomorphometry and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

5

#### Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is 10 described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhury, N. *et al. Endocrinology* (1996) 137:331-39. In this study, the immortalized cells were 15 stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 20 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of 25 luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell. Cytotoxicity can be determined by visual or microscopic examination of BMP

5 promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For *in vivo* assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing *in vivo* assay results, it may also be useful to examine

10 biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are

15 expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with

20 the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease.

25 By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone

30 healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of periodontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal  
5 osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis.  
The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing  
10 or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the  
15 compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be  
20 performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a  
25 compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well  
30 known in the art and are disclosed, for example, in Remington's Pharmaceutical

- Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms
- 5 known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.
- 10 Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods,
- 15 pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the
- 20 surface using standard surgical procedures.
- In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF),
- 25 fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (*Sampath et al. Proc. Natl. Acad. Sci. USA* (1987) 84:7109-13)
- 30 and NaF (*Tencer et al. J. Biomed. Mat. Res.* (1989) 23: 571-89) are also preferred.

Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials,

- 5 to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang *et al.* (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao *et al.* (PCT

- 10 Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander *et al.* *Ann. Surg.* (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck *et al.* *J. Bone Min. Res.* (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman *et al.* *Biomaterials* (1991) 12:619-26. Other methods well known in the art for sustained local delivery in bone include porous 15 coated metal prostheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

- The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the 20 compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be administered with an anti-resorptive compound in 25 a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

- Aqueous suspensions may contain the active ingredient in admixture with 30 pharmacologically acceptable excipients, comprising suspending agents, such as methyl

cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

- Preparations for topical and local application comprise aerosol sprays, lotions,  
5 gels and ointments in pharmaceutically appropriate vehicles which may comprise lower  
aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty  
acids, oils and fats, and silicones. The preparations may further comprise antioxidants,  
such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid  
esters.
- 10 Parenteral preparations comprise particularly sterile or sterilized products.  
Injectable compositions may be provided containing the active compound and any of  
the well known injectable carriers. These may contain salts for regulating the osmotic  
pressure.

- If desired, the osteogenic agents can be incorporated into liposomes by any of  
15 the reported methods of preparing liposomes for use in treating various pathogenic  
conditions. The present compositions may utilize the compounds noted above  
incorporated in liposomes in order to direct these compounds to macrophages,  
monocytes, other cells and tissues and organs which take up the liposomal  
composition. The liposome-incorporated compounds of the invention can be utilized  
20 by parenteral administration, to allow for the efficacious use of lower doses of the  
compounds. Ligands may also be incorporated to further focus the specificity of the  
liposomes.

- Suitable conventional methods of liposome preparation include, but are not  
limited to, those disclosed by Bangham, A.D. *et al. J Mol Biol* (1965) 23:238-252,  
25 Olson, F. *et al. Biochim Biophys Acta* (1979) 557:9-23, Szoka, F. *et al. Proc Natl  
Acad Sci USA* (1978) 75:4194-4198, Mayhew, E. *et al. \_\_\_\_\_* (1984) 775:169-  
175, Kim, S. *et al. Biochim Biophys Acta* (1983) 728:339:348, and Mayer, *et al.*  
*Biochim Biophys Acta* (1986) 858:161-168.

- The liposomes may be made from the present compounds in combination with  
30 any of the conventional synthetic or natural phospholipid liposome materials including

phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine,  
5 dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols, cholesterol hemisuccinate, glycolipids, cerebrosides, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1-  
10 (2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may  
15 be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of  
20 the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. *et al. Nature* (1980)  
288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses  
30 would include limitation or treatment of bone or cartilage deficits or defects in

domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth 5 of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either *in vitro* or *ex vivo*. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent 10 progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan *J. Orthop. Res.* (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population 15 containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in 20 need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention *ex vivo*, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be 25 immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that 30 amount which produces a statistically significant effect. For example, an "effective

- amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or
- 5 augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the
- 10 practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group.
- 15 Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.
- 20 The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to
- 25 about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

#### Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (*In vitro*)

5        This assay is similar to that described by Gowen M. & Mundy G. *J Immunol* (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration)  $\beta$ -methylcyclodextrin, wherein the medium also  
10      contains test or control substances, at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air for 96 hours.

Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three  $\mu$ m sections  
15      of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200  $\mu$ m apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

Other auxillary assays can be used as controls to determine nonBMP promoter-  
20      mediated effects of test compounds. For example, mitogenic activity can be measured using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase  
25      screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of  
30      auxillary assays.

In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth

Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2 µl/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five µm sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200 µm apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrics, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

Additional In Vivo Assays

Lead compounds can be further tested in intact animals using an *in vivo*, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, *in vivo* subcutaneous dosing assay may be conducted as follows:

In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, J. *Bone* (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. *et al.* *Calcif Tissue Intl* (1995) 56:14-18; J. Casez *et al.* *Bone and Mineral* (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogen-treated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a compound known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups of OVX animals.

Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable 5 pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day 10 cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats 15 are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as 20 placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a positive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel *et al. Endocrinology* (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar 25 vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology; and LV4 are processed for mechanical testing.

Nature of the Compounds Useful in the Invention

5 All of the compounds of the invention contain two aromatic systems, Ar<sup>1</sup> and Ar<sup>2</sup>, spaced apart by a linker at a distance of 1.5-15 Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown, Ar<sup>1</sup> and Ar<sup>2</sup> may include various preferred embodiments. These are  
10 selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety; and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if Ar<sup>1</sup> and Ar<sup>2</sup> are considered  
15 distinguishable. As will be clear, however, the designation of one aromatic system as Ar<sup>1</sup> and the other as Ar<sup>2</sup> is arbitrary; thus there are only ten possible combinations. However, for simplicity, Ar<sup>1</sup> and Ar<sup>2</sup> are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link Ar<sup>1</sup> to Ar<sup>2</sup> or *vice-versa* whether or not the complementary  
20 orientation is explicitly shown (as it is in some cases). Thus, if Ar<sup>1</sup> and Ar<sup>2</sup> are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations Ar<sup>1</sup> and Ar<sup>2</sup> are retained.

The noninterfering substituents on the aromatic system represented by Ar<sup>1</sup> and the noninterfering substituents on the aromatic system represented by Ar<sup>2</sup> are  
25 represented in the formulas herein by R<sup>a</sup> and R<sup>b</sup>, respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably 30 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents. R<sup>a</sup> and R<sup>b</sup> may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR, NR<sub>2</sub>, OOCR, COOR, NCOR, NCOOR, and benzoyl, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, N(CF<sub>3</sub>)<sub>2</sub>, NO, NO<sub>2</sub>, CN, SO, SO<sub>2</sub>R, SO<sub>3</sub>R and the like, wherein R is alkyl (1-6C) or is H.

5     Similarly, these substituents may contain R' as a substitute for R wherein R' is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where R<sup>a</sup> or R<sup>b</sup> substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

10       The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a CF<sub>3</sub> substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent  
15      or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio in combination with halo, in particular, chloro. Also preferred is the presence of a  
20      diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as  
25      hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN, CF<sub>3</sub>, OCF<sub>3</sub> and COOR, and the like.

Although the number of R<sup>a</sup> and R<sup>b</sup> may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments

include those wherein the number of R<sup>a</sup> is 0, 1 or 2 and of R<sup>b</sup> is 0, 1, 2 or 3, particularly 1 or 2.

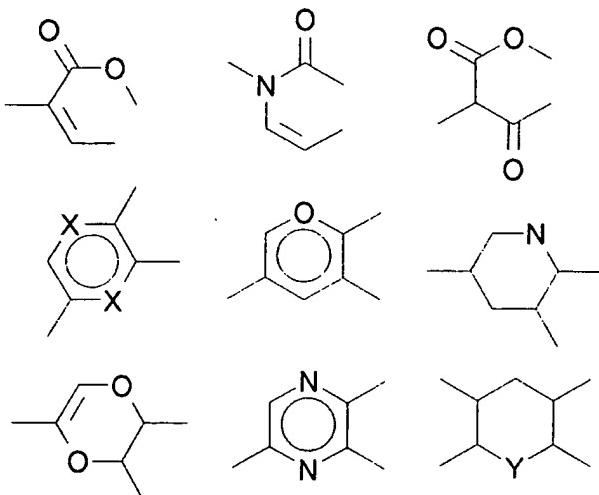
The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, 5 including those that contain cyclic moieties, that meet this spatial requirement. Useful linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for Ar<sup>1</sup> and Ar<sup>2</sup>.

As defined herein, *flexible nonconjugating* linkers are those that link only one 10 position of Ar<sup>1</sup> to one position of Ar<sup>2</sup>, and provide only a single covalent bond or a single chain between Ar<sup>1</sup> and Ar<sup>2</sup>. The chain may contain branches, but may not contain π-bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating 15 linkers, besides a covalent bond, are those of the formulas: -NR-, -CR<sub>2</sub>-, -S-, or -O-, wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas: -NRCO-, -CONR-, -CR<sub>2</sub>S-, -SCR<sub>2</sub>-, -OCR<sub>2</sub>-, -CR<sub>2</sub>O-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRSO<sub>2</sub>-, -SO<sub>2</sub>NR-, -CR<sub>2</sub>CO-, -COCR<sub>2</sub>-, and -NR-NR-CO-CR<sub>2</sub>- and its complement -CR<sub>2</sub>-CO-NR-NR-, 20 or -NRCR<sub>2</sub>CR<sub>2</sub>NR- or the thiolated counterparts, and particularly -NHCR<sub>2</sub>CR<sub>2</sub>NH-, including the isosteres thereof, such as -NRNRCSNR- and -NRNRCONR-. Also contemplated are those of the formulas: -NH(CH<sub>2</sub>)<sub>2</sub>NH-, -O(CR<sub>2</sub>)<sub>2</sub>O-, and -S(CR<sub>2</sub>)<sub>2</sub>S-, including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of Ar<sup>1</sup> and Ar<sup>2</sup>.

25 *Flexible conjugating* linkers are those that link only one position of Ar<sup>1</sup> to one position of Ar<sup>2</sup>, but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated π-bond linking system between Ar<sup>1</sup> and Ar<sup>2</sup>, thus providing for co-planarity of Ar<sup>1</sup> and Ar<sup>2</sup>. Examples of useful 30 flexible conjugating linkers include: -RC=CR-; -N=N-; -C≡C-; -RC=N-; -N=CR-;

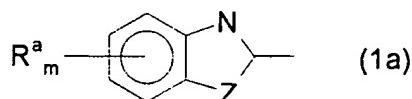
-NR-N=CR-, -NR-NR-CO-CR=CR-, -N=NCOCR<sub>2</sub>-, -N=NCSCR<sub>2</sub>-, -N=NCOCR<sub>2</sub>CR<sub>2</sub>, -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C); preferably H or lower alkyl (1-4C); and more preferably H.

*Constrained* linkers are those that have more than one point of attachment to either or both Ar<sup>1</sup> and Ar<sup>2</sup> and, thus, generally allow for only one degree of freedom. Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with Ar<sup>1</sup> and/or Ar<sup>2</sup> where either Ar<sup>1</sup> or Ar<sup>2</sup> has at least one substituent appropriately positioned to form a second covalent bond with the linker, e.g., where Ar<sup>2</sup> is a phenyl group with a reactive, ortho-positioned substituent, or is derivatized to the linker directly at the ortho position. (Although the aromatic moieties should properly be referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or "naphthyl" is used herein to include both monovalent and bivalent forms of these moieties.) Examples of particularly useful constrained linkers include

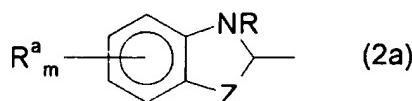


and the like, where X is O, N, S or CR, and Y is CR<sub>2</sub> or C=O.

In one class of preferred embodiments, Ar<sup>1</sup> is an aromatic system containing a 5-membered heterocycle, of the formula:



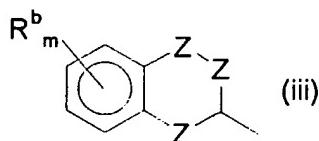
or



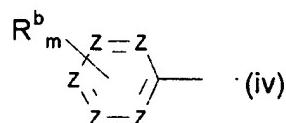
wherein Z is S, O, NR or -CR<sub>2</sub> in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional  $\pi$ -bond, each R<sup>a</sup> is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

In general, Ar<sup>2</sup> is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R<sup>b</sup>.

When Ar<sup>2</sup> is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:

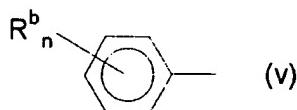


or



wherein each Z is independently a heteroatom selected from the group consisting of S, O and N; or is CR or CR<sub>2</sub>, the dotted lines represent optional  $\pi$ -bonds, each R<sup>b</sup> is independently a noninterfering substituent, and m is an integer of 0-4, with the proviso that at least one Z must be a heteroatom.

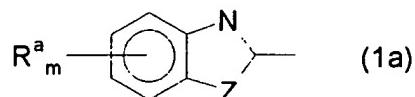
Ar<sup>2</sup> in these compounds may also have the formula



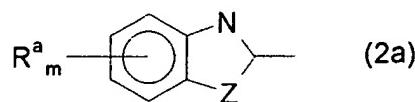
where  $R^b$  is a noninterfering substituent as defined above and  $n$  is an integer from 0 to 5.

Similarly, when  $Ar^2$  is naphthyl, it may contain 0-5  $R^b$  substitutions. When  $Ar^2$  is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for  $Ar^1$ .

Thus, in one set of preferred compounds,  $Ar^1$  is

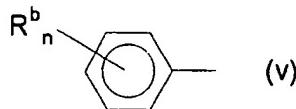


or



wherein each  $R^a$  is a noninterfering substituent,  $m$  is an integer of 0-4, the dotted line represents an optional  $\pi$  bond, and  $Z$  is O, S, NR or  $CR_2$  in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when Z is NR,  $Ar^2$  is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



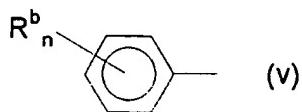
15

wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or L is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where R is H or alkyl (1-6C); and/or the dotted line represents a  $\pi$  bond.

In these embodiments as well as in alternative embodiments of Ar<sup>2</sup>, it is preferred that each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C), or R<sup>b</sup> comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and 5 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and Ar<sup>2</sup> is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula



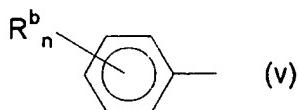
10 wherein R<sup>b</sup> is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

15 In such compounds, regardless of the choice of Ar<sup>2</sup>, preferred are those compounds wherein each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each R<sup>b</sup> is independently OR, SR or halo, where n=2 and at least one R<sup>b</sup> is independently OR or SR and/or L is -NHCO- or -CR=CR-.

Preferred compounds in this group include compounds 59-002, 59-0070, 20 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210. (See Figure 13)

25 Z can also be CR, CR<sub>2</sub> or O; here it is also preferred that Ar<sup>2</sup> is

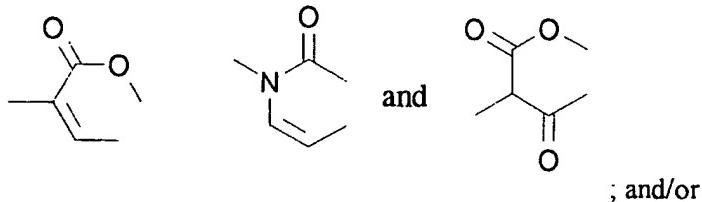


wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5, and/or L is  
 $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$   
 where R is H or alkyl (1-6C), and/or the dotted line represents a  $\pi$  bond.

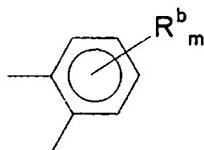
5 In these compounds, too, it is preferred that each  $R^b$  is independently halo, OR,  
 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an  
 aromatic system. A preferred compound is 896-5005. (See Figure 4)

The compounds wherein Ar<sup>1</sup> is 1a or 2a as above may also contain a  
 constrained linker.

10 In these compounds, preferred Z is S or NR; and/or those wherein L is selected  
 from the group consisting of



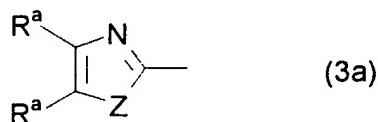
Ar<sup>2</sup> is



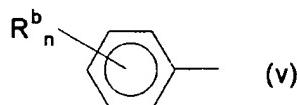
15 wherein  $R^b$  is a noninterfering substituent and m is 0-4.

Preferably, each  $R^b$  is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or  
 CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system. A preferred  
 compound is 59-0124. (See Figure 13)

In another group of preferred embodiments, Ar<sup>1</sup> is of the formula



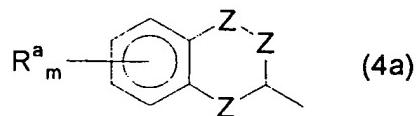
wherein each  $R^a$  is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein  $Ar^2$  is



5

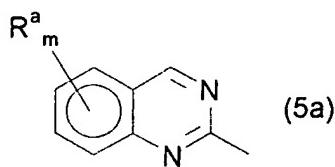
wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a  $\pi$  bond. Especially preferred are those compounds where each  $R^b$  is independently halo, OR, SR, NR<sub>2</sub>, 10 NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

In another group of compounds,  $Ar^1$  is

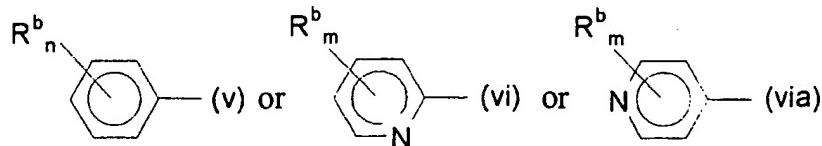


wherein  $R^a$  is a noninterfering substituent, m is an integer of 0-4, each dotted line represents an optional  $\pi$ -bond, each Z is independently N, NR, CR or CR<sub>2</sub>, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR. 15

Particularly preferred members of this group are those wherein  $Ar^1$  is



especially those wherein Ar<sub>2</sub> is

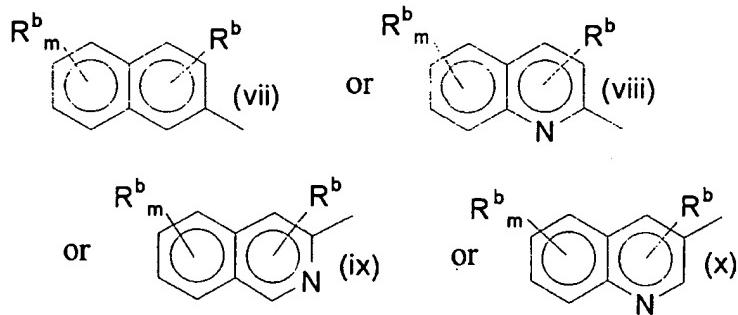


wherein each R<sup>b</sup> is independently a noninterfering substituent, and n is 0-5 and m is 0-4, and/or L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-,  
5 -NRCR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or  
-NRCOOCR<sub>2</sub>NR-.

In general, preferably each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system.

In an especially preferred group, m is 0, each R<sup>b</sup> is NR<sub>2</sub> or OR and n is 1 or 2,  
10 and/or L is -CR=CR-, -N=N- or -NRCO-, especially the compounds of formulas  
59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or  
59-0480. (See Figure 13)

Also preferred are those wherein Ar<sup>1</sup> has formula (4a) or (5a) and wherein Ar<sub>2</sub> is substituted or unsubstituted quinolyl or naphthyl of the formula



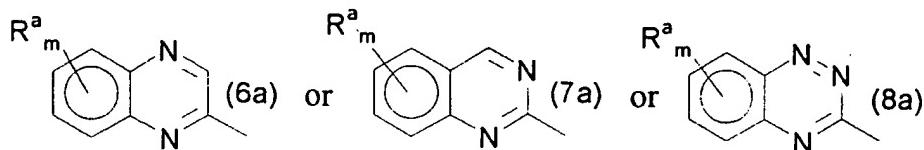
15

wherein each R<sup>b</sup> is a noninterfering substituent and m is 0-4.

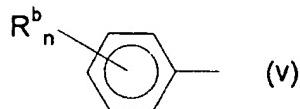
Preferred among these are those wherein L is -N=N-, -RC=CR-, -RC=N-,  
-NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-,  
-NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or -NRCOOCR<sub>2</sub>NR-, and/or wherein each R<sup>b</sup> is  
20 independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl  
(1-6C) or R<sup>b</sup> comprises an aromatic system and m is 0, 1 or 2.

The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

Ar<sup>1</sup> is also preferably



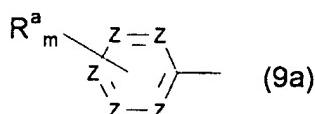
5        wherein each R<sup>a</sup> is a noninterfering substituent and m is 0-4, in particular where L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NR<sub>2</sub>R<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>NR-, -NR<sub>2</sub>CR=CRNR- or -NR<sub>2</sub>COCR<sub>2</sub>NR-, and/or Ar<sup>2</sup> is



10        wherein R<sup>b</sup> is a noninterfering substituent and n is an integer of 0-5. Especially preferred are compounds wherein each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

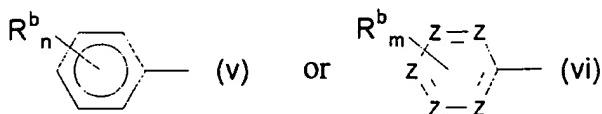
When Ar<sup>1</sup> is of formula (4a), L can also be a constrained linker.

15        In still another preferred set, Ar<sup>1</sup> is



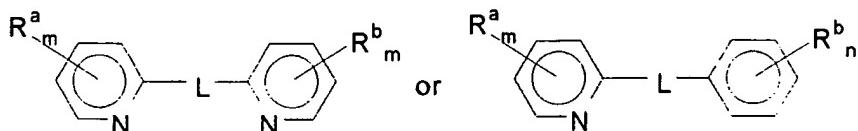
wherein each R<sup>a</sup> is independently a noninterfering substituent, m is an integer of 0-4, each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

20        In these compounds, L is preferably a flexible conjugating or nonconjugating linker, and/or wherein Ar<sup>2</sup> is



wherein each  $R^b$  is independently a noninterfering substituent, and in (vi) each  $Z$  is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

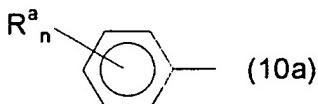
5 Preferred such compounds have the formula



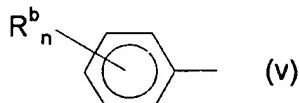
Preferred L embodiments in this group include  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOOCR_2NR-$ ; preferred for  $R^a$  and  $R^b$  are 10 halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>a</sup> or R<sup>b</sup> comprise aromatic systems and each m and n is independently 0, 1 or 2.

In particular, compounds are preferred where L is  $-NHCR_2CR_2NH-$  and R<sup>a</sup> is CF<sub>3</sub> para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See Figure 13)

15 Finally, in another preferred group, Ar<sup>1</sup> is



wherein each R<sup>a</sup> is a noninterfering substituent, and n is an integer of 0 and 5, and wherein L is a flexible linker that contains at least one nitrogen. In the alternative or in addition, Ar<sup>2</sup> is of the formula



- and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-,  
-NRCCR<sub>2</sub>CO-, -NRNRCR<sub>2</sub>CR<sub>2</sub>-, -NRNRCR=CR-, -NRNRCOCR<sub>2</sub>-,  
-NRNRCOCR=CR-, -NRNRCSCR<sub>2</sub>-, -NRNRCSCR=CR-, -NRNRCNR-,  
-NRNRCNSR-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or  
5 -NRCOCR<sub>2</sub>NR-. It is preferred that each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO,  
NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system.  
Especially preferred are those compounds wherein L is -CR=CRCNR-,  
-CR=CRCSNRNR-, -CR<sub>2</sub>CONRNR- -CR<sub>2</sub>CSNRNR-, -NRNRCNR- or  
-NRNRCNSR- and/or R<sup>b</sup> is -NR<sub>2</sub> and n=1 wherein R<sup>b</sup> is in the para position, especially  
10 wherein R<sup>a</sup> is -COOR and m is 1; most especially compounds 59-0045, 59-0095,  
59-0096, 59-0097 and 59-0098. (See Figure 13)
- As set forth above, several families of preferred embodiments are defined by specifying Ar<sup>1</sup> and Ar<sup>2</sup>, and L. In one such family, wherein Ar<sup>1</sup> is an aromatic system containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar<sup>1</sup> is  
15 unsubstituted benzothiazole, the linker (Ar<sup>1</sup> → Ar<sup>2</sup>) is NHCO, and Ar<sup>2</sup> is 2-methoxy-4-methylthiophenyl was used as a lead compound and variations of the structure studied. Figure 5 shows representative compounds synthesized to analyze the effects of the nature of the linker, various alternatives of Ar<sup>1</sup> wherein Z is O, NR or S, and the effect of substitution on the phenyl moiety, as well as the heterocycle.
- 20 Figure 5 gives the structures of these compounds, along with their maximum activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro* bone growth stimulation assay as well as the concentration at which 50% of maximum stimulation of the BMP promoter was obtained (EC<sub>50</sub>). See Example 1 for the details of this assay. The results of this study indicate that the amide linker in 59-0072 can  
25 readily be substituted by -CH=CH- and that the substitution on the phenyl ring had advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe  
>>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in the *ex vivo* calvarial assay described in Example 3.

Similar structure/activity relationship studies were conducted for compounds wherein Ar<sup>1</sup> is quinoline. In this study, compound 50-0197, wherein Ar<sup>1</sup> is unsubstituted quinoline, the linker is -CH=CH-, and Ar<sup>2</sup> is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in 5 Figure 6, along with their maximum stimulation characteristics and EC<sub>50</sub> in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline; the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar<sup>2</sup> include 2,4-di- 10 OMe; 4-NMe<sub>2</sub>-2-OMe, and 4-NMe<sub>2</sub>. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. *J Immunol* (1986) 136:2478-2482.

Another group of compounds wherein Ar<sup>1</sup> and Ar<sup>2</sup> are pyridyl heterocycles was 15 also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R<sup>a</sup> and R<sup>b</sup> were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar<sup>2</sup>. Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF<sub>3</sub> group in one of Ar<sup>1</sup> and Ar<sup>2</sup> appeared essential; 20 however, one of R<sup>a</sup> or R<sup>b</sup> could also be NO<sub>2</sub> or CN. The most preferred linker is -NHCH<sub>2</sub>CH<sub>2</sub>NH-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

Finally, a series in which Ar<sup>1</sup> is 3-carboxyphenyl was studied using 59-0045 as 25 the lead compound. In 59-0045, L is -NHN=CH- and Ar<sup>2</sup> is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R<sup>b</sup> was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098. 30 59-0098 is very active in the *ex vivo* calvarial assay described above.

Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention  
5 which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

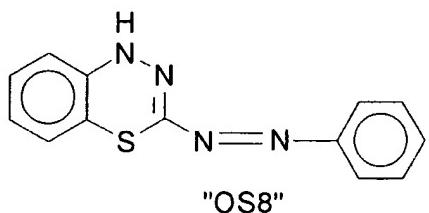
10

Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., *et al. Chem Comm* (1969) 392-393; Irving, H. N. N. H. *et al. Anal Chim Acta* (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h.  
15 After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark  
20 precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); R<sub>f</sub> 0.22) followed by recrystallization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.90 (d of d, J<sub>1</sub>=7.7, J<sub>2</sub>=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M<sup>+</sup>), 105 (26), 77 [100], 51 (27). HRMS (EI, M<sup>+</sup>) 254.0626 (calcd 25 254.0626182). Anal. Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>S: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

Example 1High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by reference. The standard positive control was 59-0008 (also denoted "OS8"), which is of the formula:



In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al.* *Endocrinology* (1996) 137:331-39, referenced above, was employed. The cells were cultured using α-MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of  $5 \times 10^3$  cells (in 50 μl)/well, and incubated for 24 hours at 37°C in 5% CO<sub>2</sub>. To initiate the assay, 50 μl of the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100 μl. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10 μM) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO<sub>2</sub>. The medium was then removed, and the cells were rinsed three times with PBS. After removal of excess PBS, 25 μl of 1X cell culture lysing reagent (Promega #E153A) was added to each well and incubated for at least ten minutes. Optionally, the plates/samples could be frozen at this point. To each well was added 50 μl of luciferase substrate (Promega #E152A; 10 ml Promega luciferase assay buffer per 7 mg Promega luciferase assay substrate). Luminescence was measured on an

automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 5 59-0008 was maximal at a concentration of approximately 3-10 µM and, more particularly, at about 3 µM, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10 µM (which value was normalized to 100). For instance, any tested compound in 10 Figure 3 and Figure 4 that showed greater activity than 10 µM of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

15

### Example 2

#### In vivo Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4- 20 fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae 25 were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day 30 range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured. There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and 5 from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

### Example 3

#### Ex vivo Calvarial Bone Growth Assay

10 A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9.  
15 In this assay, histomorphometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface. The area immediately surrounding midline suture is excluded from analysis.

20 Score

- 0 Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.
- 25 1 A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.
- 30 2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by
- 35

two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

- 5           3 A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100 $\mu\text{m}^2$ ). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less  
10           than 100 $\mu\text{m}^2$ . A score of "3+" has never been observed.

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

The results shown in Figure 9 represent those obtained when the measurements  
15           were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098  
20           and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.

#### Example 4

##### Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

25           The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5  $\mu\text{g}/\text{kg}/\text{day}$  of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50  $\mu\text{g}/\text{kg}/\text{day}$ , the first group found a 31% increase, and the second a 54% increase.

30           In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 µg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

#### Example 5

##### Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al* *Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald *et al*. *J Biol Chem* (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at  $4 \times 10^3$  cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 µl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

were assayed with 80  $\mu$ l of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methylpropanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100  $\mu$ l of 0.5 M NaOH.

5      The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

10     At day 2, compounds 59-0008 ( $10^{-9}$  M), 59-0102 ( $10^{-7}$  M) and 59-0197 ( $10^{-9}$  M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

#### Example 6

##### Synthesis of Exemplary Compounds

15     A.    Compounds of the invention wherein Ar<sup>1</sup> is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. *Synthesis* (1976) 1:37-8, using the described embodiments of Ar<sup>2</sup> and the appropriate analogous heterocycle embodied in Ar<sup>1</sup> substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.

20     Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar<sup>2</sup> is 2,4-dimethoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and 25 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline 30 product was collected by filtration.

B. Exemplary Compound 59-0150 where Ar<sup>1</sup> is of formula 4a was synthesized according to the procedure of Zamboni *et al.* *J Med Chem* (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of 5 benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added 10 and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).

15 A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the 20 cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH<sub>4</sub>Cl. This was extracted with EtAc, and the organics washed with additional NH<sub>4</sub>Cl, sat. NaHCO<sub>3</sub>, and sat. NaCl. This was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); R<sub>f</sub> 0.29), 0.135 g (26% yield) of a 25 red solid was obtained, mp=185-187 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J<sub>t</sub>=7.6, J<sub>d</sub>=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J<sub>t</sub>=7.6, J<sub>d</sub>=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J<sub>1</sub>=8.7, J<sub>2</sub>=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H).. Anal. Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O: C, 78.92; H, 6.62; N, 9.20. Found:

- C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., *Org Synth, Collect Vol V* (1973) 412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr<sub>3</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at -78°C. After 15 min, this was 5 allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R<sub>f</sub> 0.25) gave 10 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO: C, 82.57; H, 5.30; N, 5.66. Found:
- D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperidine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 µL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was 15 repeatedly extracted with ether. The organic phases were pooled, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dichloromethane:ether:hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.
- E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 20 The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with dichloromethane. The pure product was obtained as a tan powder.

F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr<sub>3</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 mL MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R<sub>f</sub> 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). <sup>1</sup>H NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO: C, 82.57; H, 5.30; N, 5.66. Found:

G. Other embodiments wherein AR<sup>1</sup> is of formula (4a) can be synthesized as follows:

a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., *et al.*, *J Org Chem* (1961) 26:2831-33; Brown, E. V.; \_\_\_\_\_ (1969) 6:571-73).

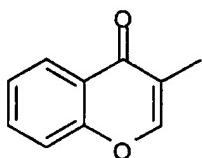
b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., *et al.*, *Chem Pharm Bull* (1977) 25:1607-09; Renault, J., *et al.*, *Hebd Seances Acad Sci, Ser C* (1975) 280:1041-43; and Lugovkin, B. P.; *Zh Obshch Khim* (1972) 42:966-69.

c. Imino derivatives may be obtained by reaction of 2-formylquinolines with anilines, Tran Quoc Son, *et al.*, (1983) 21:22-26; Hagen,

V. et al. *Pharmazie* (1983) 38:437-39; and Gershuns, A. L., et al., *Tr Kom Anal Khim, Akad Nauk SSSR* (1969) 17:242-50.

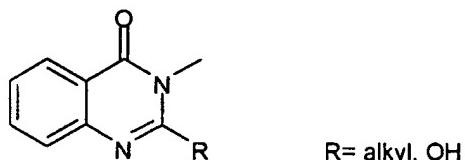
d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br<sub>2</sub> in AcOH followed by elimination with DBU as set forth in Zamboni et al. *J Med Chem* (1992) 35:3832-44.

H. Analogs having the constrained linker depicted below:



may be synthesized by reference to the methods described in Gorbuleenko, N.V. et al. *Dokl Akad Nauk Ukr SSR* (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:



may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. et al. *Synthesis* (1984) 6:520-22, and Ayyangar N. R. et al. *Dyes and Pigments* (1990) 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

dichloromethane. The product was filtered and then suspended in hot EtOAc:CHCl<sub>3</sub> (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

- 5 Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A.& Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P.& Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure  
10 O-(CH<sub>2</sub>)<sub>n</sub>-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome, G. *Heterocycles* (1990) 31:1097-104; Kameko, C. & Momose, Y. *Synthesis* (1982) 6:465-66; Tomlin, C.D.S. *et al.*, GB 1161492, published August 13, 1969.

J. Exemplary Compound 59-0097 and exemplary Compound 59-0201  
15 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was  
20 then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by  
25 substituting for at least one phenyl group the appropriate heterocycle.

K. Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH  
30

(50 µL) in EtOH:H<sub>2</sub>O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-triteträmethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 - 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.

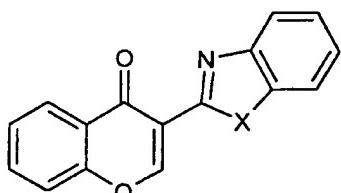
M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.

N. Exemplary Compound 59-0125 where R<sup>1</sup> is methoxy, m is 1, the linker is azo and Ar<sup>2</sup> is di(2-hydroxyethyl) amino, and related compounds having an azo

linker can be prepared in a manner similar to that described by Alberti, G. *et al. Chim Ind (Milan)* (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:

5

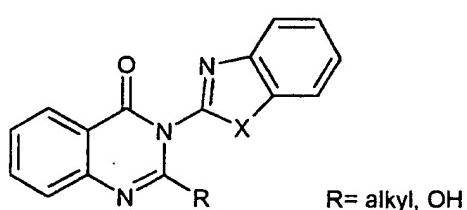


may be synthesized by reference to the methods described in Gorbuleenko, N.V.

*et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23.

10

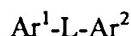
Related, constrained analogs having the structure depicted below:



may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. *et al. Synthesis* (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. *et al. Dyes and Pigments* (1990) 13:301-10.

## Claims

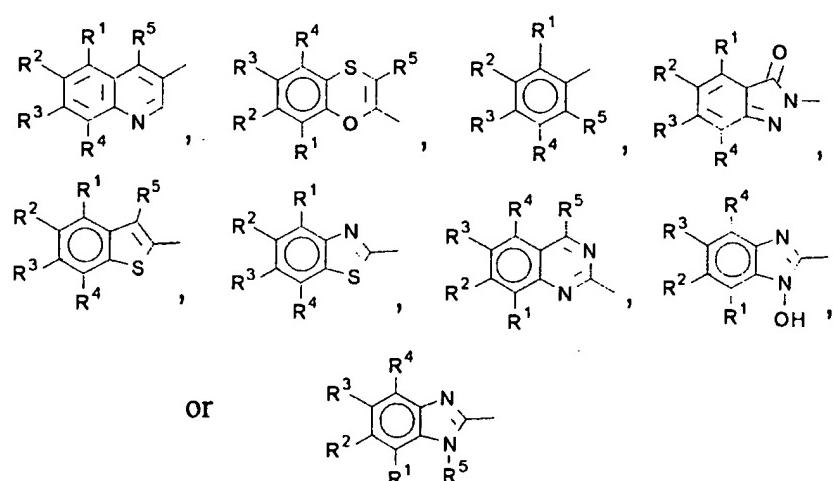
1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:



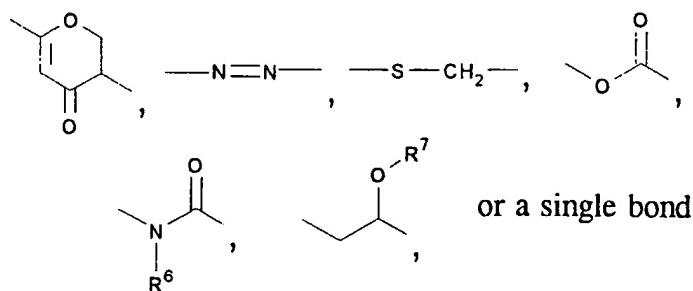
wherein each of Ar<sup>1</sup> and Ar<sup>2</sup> is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker which spaces  $\text{Ar}^1$  from  $\text{Ar}^2$  at a distance of  $1.5\text{\AA}$ - $1.8\text{\AA}$

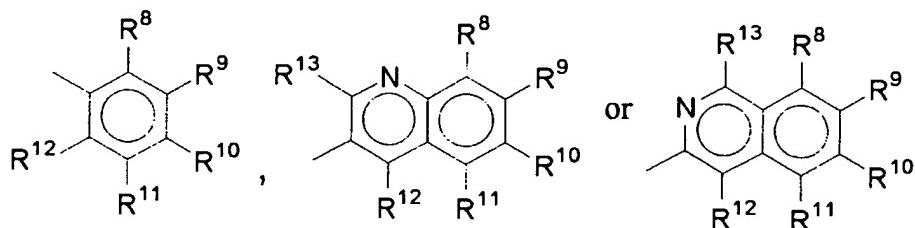
2. The method of claim 1 with the proviso that in the compound of  
15 formula (1) if  $\text{Ar}^1$  is



and L is



Ar<sup>2</sup> cannot be



wherein

- 5      R<sup>1</sup> is selected from the group consisting of:  
H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;
- 10     R<sup>2</sup> is selected from the group consisting of:  
H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;
- 15     R<sup>3</sup> is selected from the group consisting of:  
H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;
- 20     R<sup>4</sup> is selected from the group consisting of:  
H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;
- R<sup>5</sup> is selected from the group consisting of:  
H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;
- R<sup>6</sup> is selected from the group consisting of:  
H, OH, -NH<sub>2</sub>, Cl-C4 alkyl and C1-C4 alkoxy;

$R^7$  is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

$R^8$  is selected from the group consisting of:

H, OH, halo, -CF<sub>3</sub>, C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy,

5 -NHC(=O)Me and -N(C1-C4 alkyl)<sub>2</sub>;

$R^9$  is selected from the group consisting of:

H, OH, halo, -CN, -NO<sub>2</sub>, C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy,

-NHC(=O)Me and -OC(=O)Me;

$R^{10}$  is selected from the group consisting of:

10 H, OH, halo, -CN, -NO<sub>2</sub>, C1-C4 haloalkyl, -CO<sub>2</sub>H, C1-C12 alkyl, C1-C12

alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl, -NHC(=O)Me, (C1-

C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

$R^{11}$  is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl, -CF<sub>3</sub>, C1-C4 alkyl, -NH<sub>2</sub>, C1-C4 alkoxy,

15 -NHC(=O)Me, C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and  
(C1-C4)alkylcarbonyloxy;

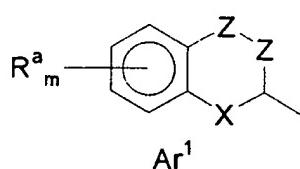
$R^{12}$  is selected from the group consisting of:

H, OH, -NH<sub>2</sub>, C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and

$R^{13}$  is selected from the group consisting of:

20 H, OH, halo, -NH<sub>2</sub>, C1-C4 alkyl, C1-C4 alkoxy -N(C1-C4)alkyl.

3. The method of claim 1 with the proviso that in the compound of formula (1), if Ar<sup>1</sup> is



25 wherein R<sup>a</sup> is a noninterfering substituent;

m is an integer of 0-4;

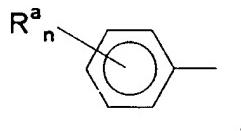
each dotted line represents an optional π-bond;

each Z is independently N, NR, O, S, CR or CR<sub>2</sub>, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO<sub>2</sub>; and

L is a flexible linker,

5 then Ar<sup>2</sup> is not a substituted or unsubstituted 6-membered aromatic ring;  
if Ar<sup>1</sup> is

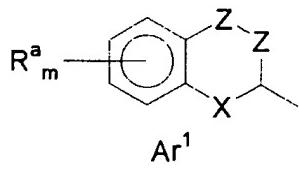


wherein R<sup>a</sup> is a noninterfering substituent;

n is an integer of 0 and 5; and

10 L is a flexible linker which does not contain nitrogen or is a constrained linker,  
then Ar<sup>2</sup> is not a substituted or unsubstituted phenyl or a substituted or  
unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of  
15 formula (1), if Ar<sup>1</sup> is



wherein R<sup>a</sup> is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

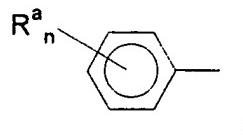
20 each Z is independently N, NR, O, S, CR or CR<sub>2</sub>, where each R is  
independently H or alkyl (1-6C);

X is O, S, SO or SO<sub>2</sub>; and

L is a flexible linker,

then Ar<sup>2</sup> is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar<sup>1</sup> is

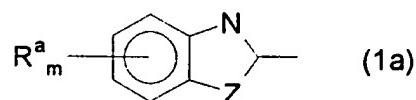


wherein R<sup>a</sup> is a noninterfering substituent;

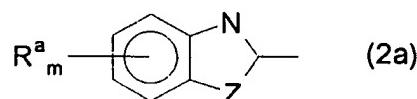
n is an integer of 0 and 5; and

5 L is a flexible linker which does not contain nitrogen or is a constrained linker,  
then Ar<sup>2</sup> is not a substituted or unsubstituted phenyl or a substituted or  
unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar<sup>1</sup> is



or



10

wherein each R<sup>a</sup> is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional π bond;

Z is O, S, NR or CR<sub>2</sub> in formula (1) or is CR in formula (2) where each R is

15 independently H or alkyl (1-6C); and

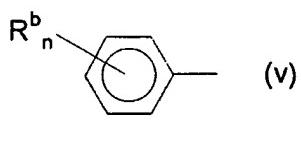
L is a flexible conjugating or nonconjugating linker or is a constrained linker.

6. The method of claim 5 wherein L is a flexible conjugating or  
nonconjugating linker.

20

7. The method of claim 6 wherein Z is NR.

8. The method of claim 7 wherein Ar<sup>2</sup> is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



wherein R<sup>b</sup> is a noninterfering substituent and n is an integer of 0-5; and/or  
5 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
-CONR- where R is H or alkyl (1-6C); and/or  
the dotted line represents a π bond.

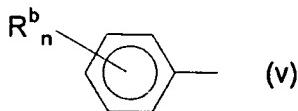
9. The method of claim 7 wherein each R<sup>b</sup> is independently halo, OR, SR,  
10 NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an  
aromatic system.

10. The method of claim 7 wherein  
m is 0; and/or  
15 each R<sup>b</sup> is independently OR, SR or halo;  
where n=2 and at least one R<sup>b</sup> is OR or SR; and/or  
L is -NHCO- or -CR=CR-.

11. The method of claim 7 wherein said compound is 59-0100, 59-103,  
20 59-104, 59-105 or 59-106.

12. The method of claim 6 wherein Z is S.

13. The method of claim 12 wherein Ar<sup>2</sup> is a substituted or unsubstituted  
25 aromatic system containing a 6-membered heterocycle or is of the formula



wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or  
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
-CONR- where R is H or alkyl (1-6C); and/or

5 the dotted line represents a  $\pi$  bond.

14. The method of claim 13 wherein each  $R^b$  is independently halo, OR,  
SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an  
aromatic system.

10

15. The method of claim 13 wherein  
m is 0; and/or  
each  $R^b$  is independently OR, SR or halo;  
where n=2 and at least one  $R^b$  is OR or SR; and/or  
15 L is -NHCO- or -CR=CR-.

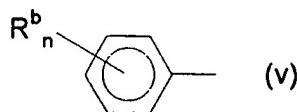
16. The method of claim 12 wherein the compound is compound number  
59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104,  
59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195,  
20 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.

17. The method of claim 16 wherein the compound is the benzothiazole  
counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.

25

18. The method of claim 6 wherein Z is CR or CR<sub>2</sub>.

19. The method of claim 18 wherein Ar<sup>2</sup> is



wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5; and/or  
 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
 -CONR- where R is H or alkyl (1-6C); and/or

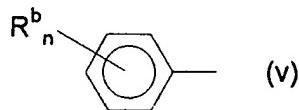
5           the dotted line represents a  $\pi$  bond.

20.       The method of claim 19 wherein each  $R^b$  is independently halo, OR,  
 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an  
 aromatic system.

10

21.       The method of claim 6 wherein Z is O.

22.       The method of claim 21 wherein Ar<sup>2</sup> is of the formula



15           wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5; and/or  
 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
 -CONR- where R is H or alkyl (1-6C); and/or  
 the dotted line represents a  $\pi$  bond.

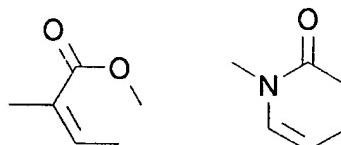
20

23.       The method of claim 19 wherein each  $R^b$  is independently halo, OR,  
 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an  
 aromatic system.

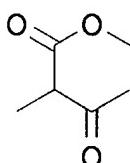
24.       The method of claim 21 wherein the compound of formula (1) is  
 25       compound number 896-5005.

25. The method of claim 5 wherein L is a constrained linker.

26. The method of claim 25 wherein Z is S or NR; and/or  
5 wherein L is selected from the group consisting of

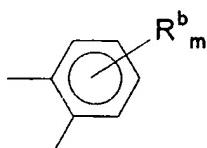


and



; and/or

wherein Ar<sup>2</sup> is



wherein R<sup>b</sup> is a noninterfering substituent and m is 0-4.

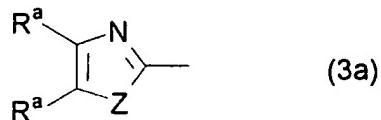
10

27. The method of claim 25 wherein each R<sup>b</sup> is independently halo, OR,  
SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or comprises an  
aromatic system.

15

28. The method of claim 25 wherein the compound of formula (1) is  
59-0124.

29. The method of any of claims 1-4 wherein Ar<sup>1</sup> is of the formula

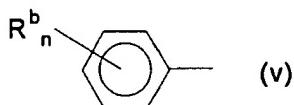


(3a)

20

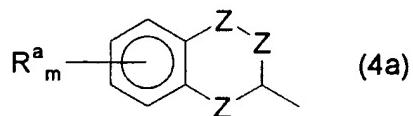
wherein each R<sup>a</sup> is independently a noninterfering substituent or is H; and  
Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or  
wherein Ar<sup>2</sup> is



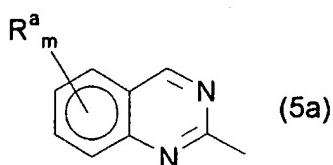
5       wherein R<sup>b</sup> is a noninterfering substituent and n is an integer of 0-5; and/or  
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
-CONR- where R is H or alkyl (1-6C); and/or  
the dotted line represents a π bond; and/or  
each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein  
10      R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar<sup>1</sup> is

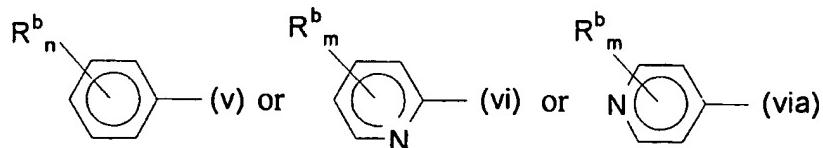


15       wherein R<sup>a</sup> is a noninterfering substituent;  
m is an integer of 0-4;  
each dotted line represents an optional π-bond;  
each Z is independently N, NR, CR or CR<sub>2</sub>, where each R is independently H  
or alkyl (1-6C) with the proviso that at least one Z is N or NR.

20       32. The method of claim 31 wherein Ar<sup>1</sup> is



33. The method of claim 31 wherein Ar<sub>2</sub> is



wherein each R<sup>b</sup> is independently a noninterfering substituent, and n is 0-5 and m is 0-4; and/or

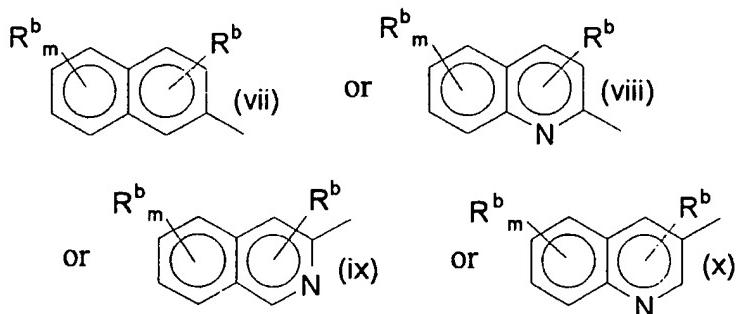
- 5       L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-,  
   -NRCR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or  
   -NRCOOCR<sub>2</sub>NR-.

34. The method of claim 33 wherein each R<sup>b</sup> is independently halo, OR,  
 10 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system.

35. The method of claim 32 wherein  
   each R<sup>b</sup> is NR<sub>2</sub> or OR and m and n are 0, 1 or 2; and/or  
 15 L is -CR=CR-, -N=N- or -NRCO-.

36. The method of claim 35 wherein the compound of formula (1) is  
 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or  
 59-0480.  
 20

37. The method of claim 31 wherein Ar<sub>2</sub> is substituted or unsubstituted quinolyl or naphthyl of the formula



wherein each  $R^b$  is a noninterfering substituent and  $m$  is 0-4.

38. The method of claim 37 wherein L is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  
 5  $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  
 $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOOCR_2NR-$ ; and/or  
 wherein each  $R^b$  is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub>  
 wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system and m is 0, 1 or 2.

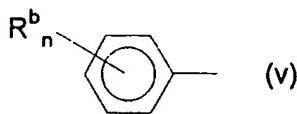
- 10 39. The method of claim 38 wherein the compound of formula (1) is  
 59-0089, 59-0090, 59-0092 or 59-0094.

40. The method of claim 31 wherein Ar<sup>1</sup> is



- 15 wherein each  $R^a$  is a noninterfering substituent and m is 0-4.

41. The method of claim 40 wherein L is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  
 $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  
 $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOOCR_2NR-$ ; and/or  
 20 Ar<sup>2</sup> is



wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or  
wherein each  $R^b$  is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub>,  
wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

5

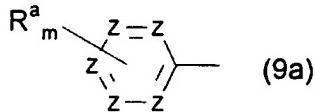
42. The method of claim 41 wherein the compound of formula (1) is  
59-203, 59-285 or 59-286.

10

43. The method of claim 31 wherein L is a constrained linker.

10

44. The method of any of claims 1-4 wherein Ar<sup>1</sup> is



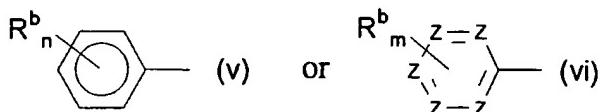
15

wherein each  $R^a$  is independently a noninterfering substituent;  
 $m$  is an integer of 0-4;  
each Z is independently N or CR, where R is H or alkyl (1-6C), with the  
proviso that at least one Z must be N and at least one Z must be CR.

20

45. The method of claim 44 wherein L is a flexible conjugating or  
nonconjugating linker; and/or

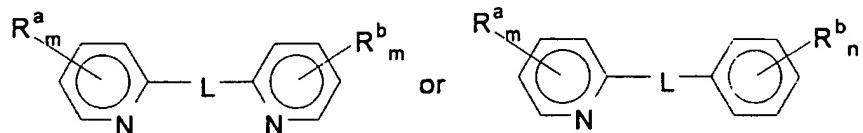
wherein Ar<sup>2</sup> is



wherein each  $R^b$  is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the  
5 formula

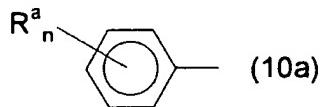


47. The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-,  
-NRCO-, -NRCR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-,  
10 -NR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or -NRCOCR<sub>2</sub>NR-; and/or  
wherein each R<sup>a</sup> and R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub>  
or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system and each m  
and n is independently 0, 1 or 2.

15 48. The method of claim 47 wherein L is -NHCR<sub>2</sub>CR<sub>2</sub>NH-, m is 1 and R<sup>a</sup> is  
CF<sub>3</sub> para to L.

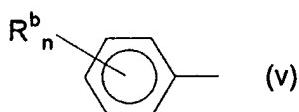
49. The method of claim 48 wherein the compound of formula (1) is  
59-0145, 59-0450, 59-0459 or 59-0483.

20 50. The method of any of claims 1-4 wherein Ar<sup>1</sup> is



wherein each R<sup>a</sup> is a noninterfering substituent; and  
n is an integer of 0 and 5, and  
25 wherein L is a flexible linker that contains at least one nitrogen; and/or

wherein  $\text{Ar}^2$  is of the formula



and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>-,  
-NCR<sub>2</sub>CO-, -NRNRCR<sub>2</sub>CR<sub>2</sub>-, -NRNRCR=CR-, -NRNRCOCR<sub>2</sub>-,  
5 -NRNRCOCR=CR-, -NRNRCSCR<sub>2</sub>-, -NRNRCSCR=CR-, -NRNRCCONR-,  
-NRNRCNSNR-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or  
-NRCOCR<sub>2</sub>NR-.

51. The method of claim 50 wherein each  $R^b$  is independently halo, OR,  
10 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

52. The method of claim 50 wherein L is -CR=CRCONRNR-,  
-CR=CRCSNRNR-, -CR<sub>2</sub>CONRNR- -CR<sub>2</sub>CSNRNR-, -NRNRCONR- or  
15 -NRNRCNSNR- and/or

$R^b$  is -NR<sub>2</sub> and n=1 wherein  $R^b$  is in the para position.

53. The method of claim 50 wherein  $R^a$  is -COOR and m is 1.  
20 54. The method of claim 52 wherein the compound of formula (1) is  
59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.

55. A pharmaceutical composition for use in a method to treat a condition  
in a vertebrate animal characterized by a deficiency in, or need for, bone growth  
25 replacement and/or an undesirable level of bone resorption which composition contains  
a pharmaceutically acceptable excipient and an effective amount of a compound of the  
formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which method comprises administering said composition to a vertebrate subject, said compound set forth in any preceding claim.

1 / 146

$\text{Ar}^1 - \text{linker} - \text{Ar}^2$ 1.5 - 15 Å		(I)
$\text{Ar}^1$	$\text{Ar}^2$	
contains 5-membered heterocycle	substituted or unsubstituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-B
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	II-H
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II-I
substituted or unsubstituted benzene	substituted or unsubstituted benzene	II-J

Figure 1

2 / 146

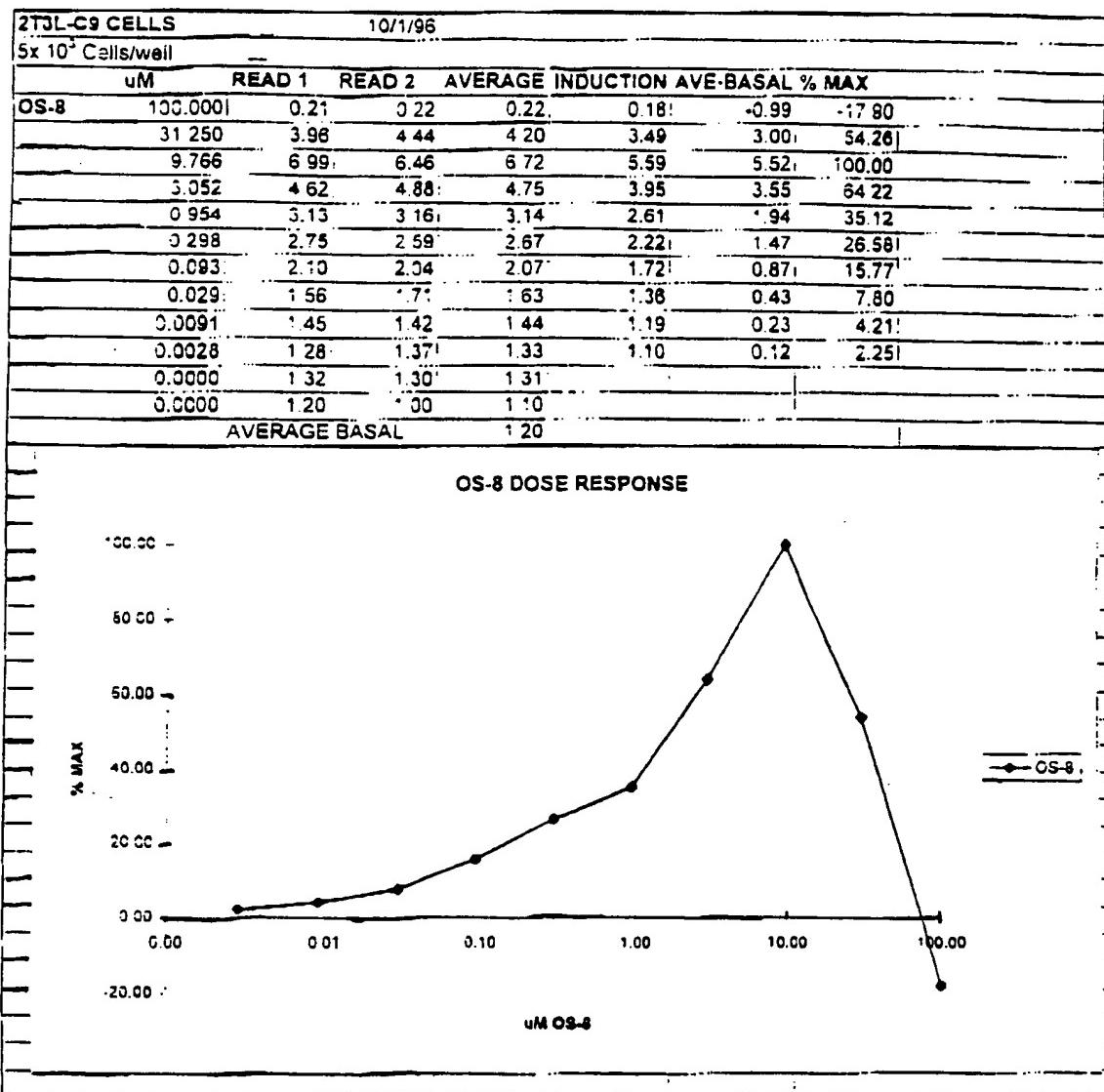


Figure 2

3/146

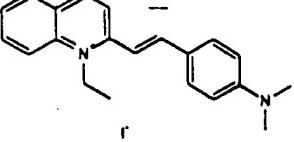
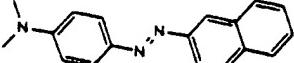
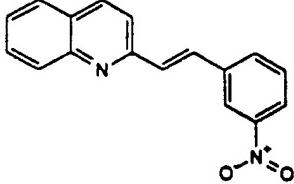
NNC#	MOL.WEIGHT	Concentration	% Response
	430.33		
50-0194		100.00 μM	-19.190
		31.25 μM	32.450
		9.77 μM	-14.240
		3.05 μM	-11.330
		953.67 nM	-12.780
		298.02 nM	-13.450
		93.13 nM	-12.290
		29.10 nM	-9.440
		9.09 nM	-6.450
		2.84 nM	-6.130
		888.18 pM	-3.320
	275.36		
50-0195		100.00 μM	-4.630
		31.25 μM	16.790
		9.77 μM	62.830
		3.05 μM	102.720
		953.67 nM	60.860
		298.02 nM	32.450
		93.13 nM	19.340
		29.10 nM	17.220
		9.09 nM	5.640
		2.84 nM	4.840
		888.18 pM	5.640
	276.30		
50-0196		100.00 μM	-16.210
		31.25 μM	-8.560
		9.77 μM	11.620
		3.05 μM	27.790
		953.67 nM	16.390
		298.02 nM	6.230
		93.13 nM	12.420
		29.10 nM	12.630
		9.09 nM	6.590
		2.84 nM	7.970
		888.18 pM	5.060

Figure 3

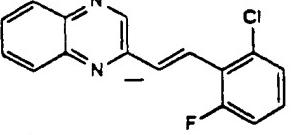
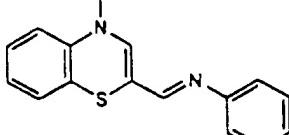
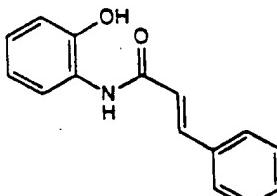
4 / 146

<chem>CN(C)c1ccc(CC=CC2=Cc3ccccc3N=C2)cc1</chem>	274.37				
50-0197	100.00 $\mu\text{M}$	-18.250			
50-0197	31.25 $\mu\text{M}$	-14.980			
	9.77 $\mu\text{M}$	4.040			
	3.05 $\mu\text{M}$	93.790			
	953.67 $\text{nM}$	205.530			
	298.02 $\text{nM}$	242.920			
	93.13 $\text{nM}$	195.880			
	29.10 $\text{nM}$	115.320			
	9.09 $\text{nM}$	85.830			
	2.84 $\text{nM}$	54.380			
	888.18 $\text{pM}$	33.180			
<chem>CN(C)c1ccc(CC=CC2=Cc3ccccc3N=N2)cc1</chem>	254.32				
59-0008					
<chem>CN(C)c1ccc(CC=CC2=Cc3ccncc3N=N2)cc1</chem>	59-0019				
59-0019	100.00 $\mu\text{M}$	-22.240			
59-0019	31.25 $\mu\text{M}$	-22.670			
	9.77 $\mu\text{M}$	-17.470			
	3.05 $\mu\text{M}$	74.490			
	953.67 $\text{nM}$	198.080			
	298.02 $\text{nM}$	258.340			
	93.13 $\text{nM}$	225.350			
	29.10 $\text{nM}$	75.220			
	9.09 $\text{nM}$	24.030			
	2.84 $\text{nM}$	34.480			
	888.18 $\text{pM}$	-3.740			
<chem>CN(C)c1ccc(CC=CC2=Cc3ccncc3Cl)cc1</chem>	268.73				
59-0020					
59-0020	100.00 $\mu\text{M}$	-18.510			
59-0020	31.25 $\mu\text{M}$	-16.040			
	9.77 $\mu\text{M}$	-0.270			
	3.05 $\mu\text{M}$	99.490			
	953.67 $\text{nM}$	153.320			
	298.02 $\text{nM}$	110.240			
	93.13 $\text{nM}$	60.030			

5 / 146

	29.10 nM	37.870
	9.09 nM	24.820
	2.84 nM	20.500
	888.18 pM	13.310

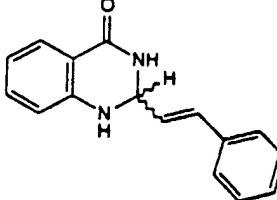
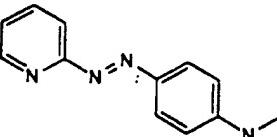
6/146

	284.72			
59-0021	100.00 μM	-16.310		
	31.25 μM	-12.850		
	9.77 μM	84.130		
	3.05 μM	89.940		
	953.67 nM	65.760		
	298.02 nM	33.940		
	93.13 nM	22.560		
	29.10 nM	25.020		
	9.09 nM	13.910		
	2.84 nM	33.270		
	888.18 pM	15.500		
	268.37			
59-0022	100.00 μM	7.250		
	31.25 μM	-2.070		
	9.77 μM	-0.270		
	3.05 μM	4.390		
	953.67 nM	3.060		
	298.02 nM	-1.800		
	93.13 nM	-0.200		
	29.10 nM	-3.270		
	9.09 nM	1.130		
	2.84 nM	2.590		
	888.18 pM	2.460		
	239.28			
59-0023	100.00 μM	-12.720		
	31.25 μM	33.140		
	9.77 μM	56.500		
	3.05 μM	29.550		
	953.67 nM	25.380		
	298.02 nM	15.700		
	93.13 nM	7.380		
	29.10 nM	-9.710		
	9.09 nM	1.000		
	2.84 nM	4.520		
	888.18 pM	-0.010		

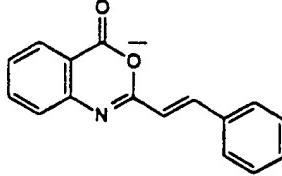
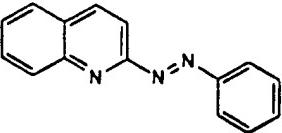
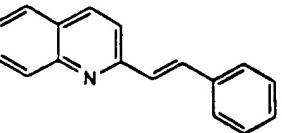
7/146

<chem>C=CC(c1ccccc1)c2[nH]c3ccccc23</chem>	59-0024	220.28				
<chem>C=CC(c1ccccc1)N(C)c2ccncc2</chem>	59-0025	224.31				
59-0025		100.00   uM	-25.590			
		31.25   uM	14.150			
		9.77   uM	50.690			
		3.05   uM	57.880			
		953.67   nM	38.900			
		298.02   nM	28.530			
		93.13   nM	19.660			
		29.10   nM	17.490			
		9.09   nM	-0.600			
		2.84   nM	-4.180			
		888.18   pM	4.870			
<chem>N#Cc1ccccc1N=Nc2ccncc2</chem>	59-0026	248.29				
59-0026		100.00   uM	-29.830			
		31.25   uM	-9.440			
		9.77   uM	-10.470			
		3.05   uM	46.220			
		953.67   nM	107.760			
		298.02   nM	86.720			
		93.13   nM	36.850			
		29.10   nM	26.720			
		9.09   nM	8.520			
		2.84   nM	-1.240			
		888.18   pM	4.020			

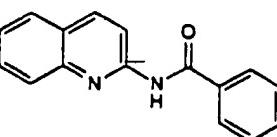
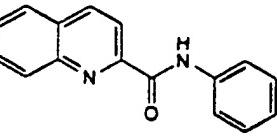
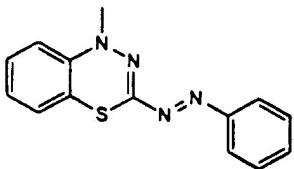
8/146

					
59-0027	250.30				
59-0027		100.00 μM	89.8101		
		31.25 μM	54.6701		
		9.77 μM	44.9401		
		3.05 μM	23.7801		
		953.67 nM	8.3801		
		298.02 nM	6.3301		
		93.13 nM	7.3601		
		29.10 nM	3.3801		
		9.09 nM	-1.6201		
		2.84 nM	-3.6701		
		888.18 pM	-0.7201		
					
59-0028	226.28				
59-0028		100.00 μM	-26.7501		
		31.25 μM	-16.7401		
		9.77 μM	29.5501		
		3.05 μM	100.5801		
		953.67 nM	54.9401		
		298.02 nM	31.3401		
		93.13 nM	7.5001		
		29.10 nM	7.5001		
		9.09 nM	7.8801		
		2.84 nM	3.1401		
		888.18 pM	4.6701		

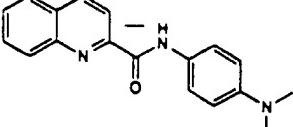
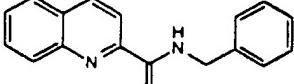
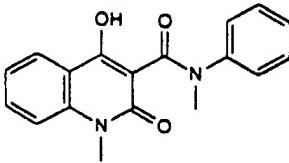
9/146

					
59-0029	249.27				
59-0029		100.00 μM	-15.160		
		31.25 μM	41.940		
		9.77 μM	36.630		
		3.05 μM	7.120		
		953.67 nM	21.880		
		298.02 nM	15.540		
		93.13 nM	1.810		
		29.10 nM	1.370		
		9.09 nM	12.140		
		2.84 nM	-4.230		
		888.18 pM	9.040		
					
59-0030A	233.28				
59-0030 A		100.00 μM	-27.970		
		31.25 μM	-22.830		
		9.77 μM	-5.420		
		3.05 μM	57.280		
		953.67 nM	72.620		
		298.02 nM	53.000		
		93.13 nM	29.990		
		29.10 nM	14.630		
		9.09 nM	3.870		
		2.84 nM	6.970		
		888.18 pM	1.810		
					
59-0031	231.30				
59-0031		100.00 μM	-25.790		
		31.25 μM	-17.810		
		9.77 μM	20.840		
		3.05 μM	87.380		
		953.67 nM	49.320		
		298.02 nM	43.110		
		93.13 nM	29.530		
		29.10 nM	1.810		
		9.09 nM	1.220		
		2.84 nM	-0.550		
		888.18 pM	4.160		

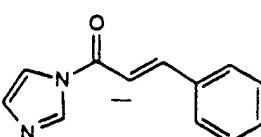
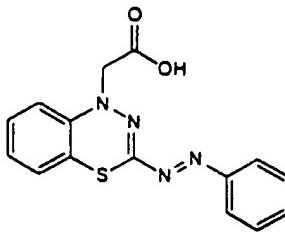
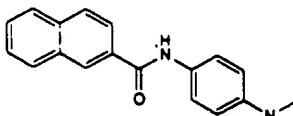
10 / 146

					
59-0032	248.29				
59-0032		100.00 uM	-7.780		
		31.25 uM	40.750		
		9.77 uM	42.820		
		3.05 uM	25.700		
		953.67 nM	31.170		
		298.02 nM	34.410		
		93.13 nM	3.570		
		29.10 nM	4.320		
		9.09 nM	-10.000		
		2.84 nM	5.650		
		888.16 pM	11.990		
					
59-0033	248.29				
59-0033		100.00 uM	-28.180		
		31.25 uM	-11.590		
		9.77 uM	55.300		
		3.05 uM	49.710		
		953.67 nM	47.410		
		298.02 nM	0.250		
		93.13 nM	7.980		
		29.10 nM	-8.940		
		9.09 nM	-7.630		
		2.84 nM	-0.400		
		888.18 pM	-5.980		
					
59-0034	268.34				
59-0034		100.00 uM	-28.51		
		31.25 uM	24		
		9.77 uM	73.58		
		3.05 uM	37.91		
		953.67 nM	20.09		
		298.02 nM	16.87		
		93.13 nM	15.23		
		29.10 nM	28.83		
		9.09 nM	9.08		
		2.84 nM	-23.02		
		888.18 pM	-0.32		

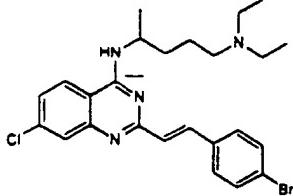
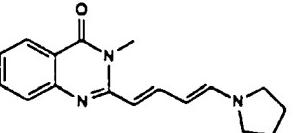
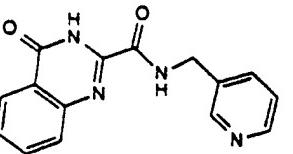
11 / 146

				
59-0035	291.36			
59-0035	100.00 μM	-14.92		
	31.25 μM	29.17		
	9.77 μM	15.87		
	3.05 μM	18.61		
	953.67 nM	3.88		
	298.02 nM	6.15		
	93.13 nM	3.22		
	29.10 nM	-10.03		
	9.09 nM	15.56		
	2.84 nM	-3.56		
	888.18 pM	-7.13		
				
59-0036	262.31			
59-0036	100.00 μM	-0.98		
	31.25 μM	-3.25		
	9.77 μM	-4.54		
	3.05 μM	-1.95		
	953.67 nM	0.32		
	298.02 nM	-6.49		
	93.13 nM	-17.19		
	29.10 nM	-0.66		
	9.09 nM	-5.52		
	2.84 nM	-9.41		
	888.18 pM	-16.53		
				
59-0037	308.00			
59-0037	100.00 μM	-10.69		
	31.25 μM	-11.99		
	9.77 μM	-10.03		
	3.05 μM	-19.11		
	953.67 nM	-9.41		
	298.02 nM	2.27		
	93.13 nM	-2.91		
	29.10 nM	-10.69		
	9.09 nM	2.59		
	2.84 nM	-0.66		
	888.18 pM	-2.59		

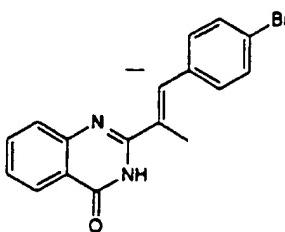
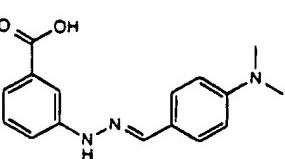
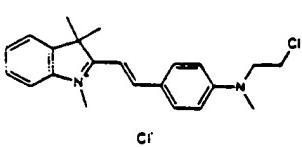
12 / 146

				
59-0038	291.36			
59-0038	100.00   uM	-23.430		
	31.25   uM	-8.390		
	9.77   uM	-0.100		
	3.05   uM	-2.880		
	953.67   nM	-2.240		
	298.02   nM	3.900		
	93.13   nM	6.350		
	29.10   nM	1.150		
	9.09   nM	6.960		
	2.84   nM	-4.390		
	888.18   pM	-0.380		
				
59-0039	312.35			
59-0039	100.00   uM	14.170		
	31.25   uM	7.620		
	9.77   uM	1.940		
	3.05   uM	-3.140		
	953.67   nM	-7.770		
	298.02   nM	-5.980		
	93.13   nM	-8.820		
	29.10   nM	-2.390		
	9.09   nM	-16.580		
	2.84   nM	-4.480		
	888.18   pM	-0.450		
				
59-0040	290.37			
59-0040	100.00   uM	-20.400		
	31.25   uM	-17.310		
	9.77   uM	-8.110		
	3.05   uM	32.160		
	953.67   nM	36.180		
	298.02   nM	17.440		
	93.13   nM	2.040		
	29.10   nM	10.350		
	9.09   nM	-6.070		
	2.84   nM	6.960		
	888.18   pM	13.440		

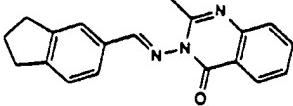
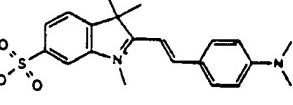
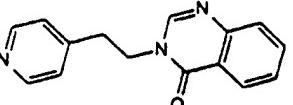
13 / 146

				
59-0041	501.90			
59-0041	100.00 μM	-18.37		
	31.25 μM	-17.33		
	9.77 μM	-5.11		
	3.05 μM	3.31		
	953.67 nM	-0.77		
	298.02 nM	-1.56		
	93.13 nM	3.55		
	29.10 nM	-11.24		
	9.09 nM	0.25		
	2.84 nM	-0.27		
	888.18 pM	2.02		
				
59-0042	281.36			
59-0042	100.00 μM	183.51		
	31.25 μM	-7.67		
	9.77 μM	9.41		
	3.05 μM	0.75		
	953.67 nM	8.11		
	298.02 nM	3.82		
	93.13 nM	2.54		
	29.10 nM	4.07		
	9.09 nM	-9.73		
	2.84 nM	-0.02		
	888.18 pM	18.37		
				
59-0043	280.29			
59-0043	100.00 μM	20.66		
	31.25 μM	7.4		
	9.77 μM	-1.29		
	3.05 μM	-2.31		
	953.67 nM	1.54		
	298.02 nM	-0.79		
	93.13 nM	1.52		
	29.10 nM	2.79		
	9.09 nM	-0.27		
	2.84 nM	8.92		
	888.18 pM	-4.34		

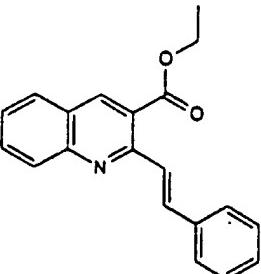
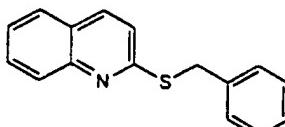
14/146

				
59-0044	341.21			
59-0044	100.00 $\mu\text{M}$	7.38		
	31.25 $\mu\text{M}$	11.72		
	9.77 $\mu\text{M}$	12.49		
	3.05 $\mu\text{M}$	-0.52		
	953.67 $\text{nM}$	0.5		
	298.02 $\text{nM}$	6.11		
	93.13 $\text{nM}$	-1.54		
	29.10 $\text{nM}$	19.14		
	9.09 $\text{nM}$	7.13		
	2.84 $\text{nM}$	-2.06		
	888.18 $\text{pM}$	5.84		
				
59-0045	283.33			
59-0045	100.00 $\mu\text{M}$	52.37	64.460	
	31.25 $\mu\text{M}$	148.43	192.960	
	9.77 $\mu\text{M}$	204.47	422.540	
	3.05 $\mu\text{M}$	280.3	437.020	
	953.67 $\text{nM}$	254.82	410.890	
	298.02 $\text{nM}$	218.21	268.090	
	93.13 $\text{nM}$	196.98	183.730	
	29.10 $\text{nM}$	96.06	80.440	
	9.09 $\text{nM}$	67.35	55.530	
	2.84 $\text{nM}$	52.99	44.160	
				
59-0046	389.37			
59-0046	100.00 $\mu\text{M}$	79.33		
	31.25 $\mu\text{M}$	2.24		
	9.77 $\mu\text{M}$	-1.67		
	3.05 $\mu\text{M}$	-6.18		
	953.67 $\text{nM}$	0.001		
	298.02 $\text{nM}$	-3.63		
	93.13 $\text{nM}$	-0.84		
	29.10 $\text{nM}$	-6.42		
	9.09 $\text{nM}$	-3.92		
	2.84 $\text{nM}$	0.3		
	888.18 $\text{pM}$	5.61		

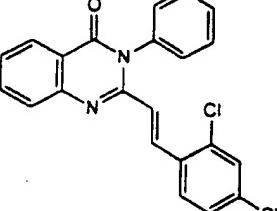
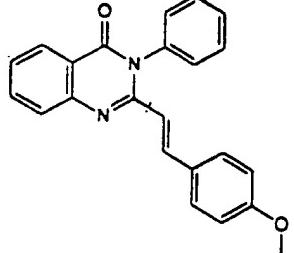
15 / 146

				
59-0047	303.37			
59-0047		100.00 μM	-6.73	
		31.25 μM	10.38	
		9.77 μM	-8.16	
		3.05 μM	-1.39	
		953.67 nM	-10.11	
		298.02 nM	-4.49	
		93.13 nM	-7.28	
		29.10 nM	-12.34	
		9.09 nM	-3.08	
		2.84 nM	-2.26	
		888.18 pM	-5.34	
				
59-0048	384.50			
59-0048		100.00 μM	-6.73	
		31.25 μM	0.27	
		9.77 μM	-5.81	
		3.05 μM	-2.26	
		953.67 nM	-12.89	
		298.02 nM	-1.69	
		93.13 nM	-4.77	
		29.10 nM	-8.14	
		9.09 nM	-3.92	
		2.84 nM	-11.21	
		888.18 pM	-4.77	
				
59-0049	251.29			
59-0049		100.00 μM	4.49	
		31.25 μM	0	
		9.77 μM	-4.77	
		3.05 μM	1.96	
		953.67 nM	8.69	
		298.02 nM	-5.04	
		93.13 nM	-2.24	
		29.10 nM	1.69	
		9.09 nM	-4.49	
		2.84 nM	2.24	
		888.18 pM	-0.31	

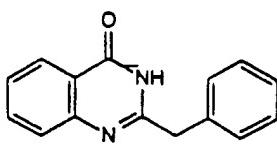
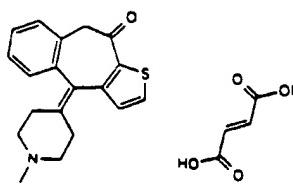
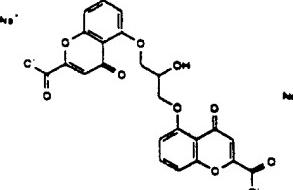
16 / 146

					
59-0050	303.36				
59-0050		100.00 μM	45.79		
		31.25 μM	10.02		
		9.77 μM	11.29		
		3.05 μM	-4.68		
		953.67 nM	-6.92		
		298.02 nM	-5.65		
		93.13 nM	1.69		
		29.10 nM	-7.57		
		9.09 nM	-12.05		
		2.84 nM	-13.63		
		888.18 pM	5.2		
					
59-0051	251.35				
59-0051		100.00 μM	32.36		
		31.25 μM	-18.42		
		9.77 μM	-0.55		
		3.05 μM	-13.94		
		953.67 nM	-12.02		
		298.02 nM	-14.59		
		93.13 nM	-7.55		
		29.10 nM	-11.4		
		9.09 nM	-14.91		
		2.84 nM	-10.74		
		888.18 pM	-20.03		

17/146

					
59-0052	393.28				
59-0052		100.00 μM	-21.62		
		31.25 μM	-13.32		
		9.77 μM	-21.31		
		3.05 μM	-11.08		
		953.67 nM	-20.66		
		298.02 nM	-17.14		
		93.13 nM	-16.49		
		29.10 nM	-11.4		
		9.09 nM	-10.74		
		2.84 nM	-11.08		
		888.18 pM	-14.59		
					
59-0053	354.41				
59-0053		100.00 μM	-17.14		
		31.25 μM	-21.31		
		9.77 μM	-9.47		
		3.05 μM	-11.08		
		953.67 nM	-0.83		
		298.02 nM	-11.4		
		93.13 nM	-9.47		
		29.10 nM	-19.72		
		9.09 nM	-18.45		
		2.84 nM	-10.09		
		888.18 pM	-2.76		

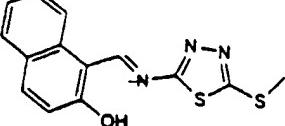
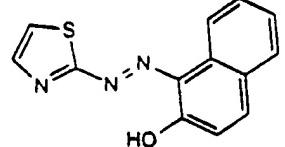
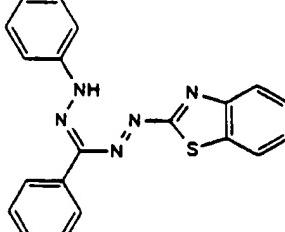
18/146

				
59-0054	236.28			
59-0054	100.00 μM	-20.04		
	31.25 μM	-6.95		
	9.77 μM	8.31		
	3.05 μM	-3.37		
	953.67 nM	-2.41		
	298.02 nM	-0.99		
	93.13 nM	-0.99		
	29.10 nM	-1.94		
	9.09 nM	5.92		
	2.84 nM	-2.17		
	888.18 pM	-9.31		
				
59-0055	425.51			
59-0055	100.00 μM	-13.76		
	31.25 μM	-9.51		
	9.77 μM	-2.02		
	3.05 μM	3.24		
	953.67 nM	-6.27		
	298.02 nM	-4.05		
	93.13 nM	-1.82		
	29.10 nM	-7.49		
	9.09 nM	-7.09		
	2.84 nM	-3.04		
				
59-0056	512.34			
59-0056	100.00 μM	-1.42		
	31.25 μM	-4.87		
	9.77 μM	0.18		
	3.05 μM	3.84		
	953.67 nM	-5.07		
	298.02 nM	-7.29		
	93.13 nM	0.001		
	29.10 nM	-4.25		
	9.09 nM	-1.02		
	2.84 nM	-3.85		

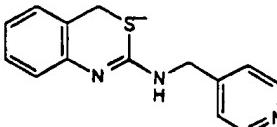
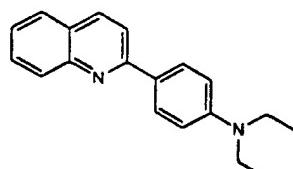
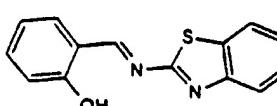
19 / 146

59-0057				
59-0057	100.00 μM	-24.150		
	31.25 μM	-24.300		
	9.77 μM	-5.980		
	3.05 μM	-11.500		
	953.67 nM	-13.000		
	298.02 nM	-6.280		
	93.13 nM	-12.550		
	29.10 nM	-6.870		
	9.09 nM	-8.520		
	2.84 nM	-16.290		
59-0058				
59-0058	100.00 μM	4.170		
	31.25 μM	7.620		
	9.77 μM	-1.790		
	3.05 μM	-7.320		
	953.67 nM	-1.940		
	298.02 nM	-6.870		
	93.13 nM	-1.490		
	29.10 nM	-8.370		
	9.09 nM	-5.080		
	2.84 nM	-12.400		
59-0059				
59-0059	100.00 μM	-18.770		
	31.25 μM	-16.140		
	9.77 μM	-3.090		
	3.05 μM	0.150		
	953.67 nM	6.010		
	298.02 nM	-1.910		
	93.13 nM	-1.760		
	29.10 nM	-9.100		
	9.09 nM	-8.220		
	2.84 nM	-5.720		

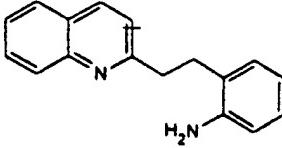
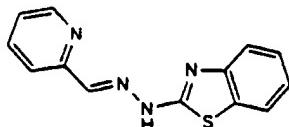
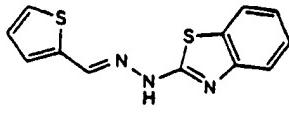
20 / 146

				
59-0060				
59-0060	100.00 μM	-4.250		
	31.25 μM	-14.520		
	9.77 μM	1.030		
	3.05 μM	-1.180		
	953.67 nM	-13.200		
	298.02 nM	-0.740		
	93.13 nM	-3.670		
	29.10 nM	-7.340		
	9.09 nM	-1.310		
	2.84 nM	0.290		
				
59-0061				
59-0061	100.00 μM	-17.890		
	31.25 μM	-18.770		
	9.77 μM	-17.170		
	3.05 μM	-14.080		
	953.67 nM	-17.020		
	298.02 nM	-7.190		
	93.13 nM	-1.910		
	29.10 nM	-0.440		
	9.09 nM	-6.010		
	2.84 nM	-4.560		
				
59-0062				
59-0062	100.00 μM	-13.940		
	31.25 μM	-12.910		
	9.77 μM	-4.560		
	3.05 μM	-4.540		
	953.67 nM	-6.900		
	298.02 nM	-4.100		
	93.13 nM	-1.620		
	29.10 nM	3.230		

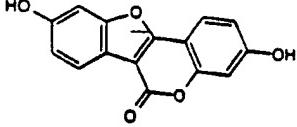
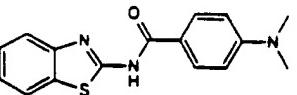
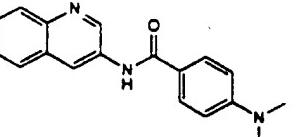
21/146

		9.09 nM	8.070
		2.84 nM	0.440
	59-0063		
59-0063		100.00 μM	-2.510
		31.25 μM	-6.130
		9.77 μM	-8.950
		3.05 μM	-8.020
		953.67 nM	-8.010
		298.02 nM	-2.520
		93.13 nM	-5.810
		29.10 nM	-3.450
		9.09 nM	-4.390
		2.84 nM	-6.280
	59-0064		
59-0064		100.00 μM	-23.090
		31.25 μM	-21.040
		9.77 μM	78.400
		3.05 μM	155.220
		953.67 nM	113.120
		298.02 nM	30.640
		93.13 nM	15.240
		29.10 nM	22.150
		9.09 nM	-0.770
		2.84 nM	4.410
	59-0065		
59-0065		100.00 μM	-2.030
		31.25 μM	-2.980
		9.77 μM	-15.240
		3.05 μM	-15.400
		953.67 nM	-15.240
		298.02 nM	-10.520
		93.13 nM	-13.830
		29.10 nM	-5.810
		9.09 nM	-3.620
		2.84 nM	-7.070

22/146

				
59-0066				
59-0066	100.00 $\mu\text{M}$	10.060		
	31.25 $\mu\text{M}$	2.580		
	9.77 $\mu\text{M}$	10.850		
	3.05 $\mu\text{M}$	14.610		
	953.87 $\text{nM}$	0.950		
	298.02 $\text{nM}$	3.780		
	93.13 $\text{nM}$	1.730		
	29.10 $\text{nM}$	-2.620		
	9.09 $\text{nM}$	-2.620		
	2.84 $\text{nM}$	-3.920		
				
59-0067				
59-0067	100.00 $\mu\text{M}$	-24.040		
	31.25 $\mu\text{M}$	-24.890		
	9.77 $\mu\text{M}$	-1.450		
	3.05 $\mu\text{M}$	60.900		
	953.87 $\text{nM}$	133.860		
	298.02 $\text{nM}$	75.330		
	93.13 $\text{nM}$	28.760		
	29.10 $\text{nM}$	20.070		
	9.09 $\text{nM}$	4.980		
	2.84 $\text{nM}$	4.450		
				
59-0068				
59-0068	100.00 $\mu\text{M}$	-22.130		
	31.25 $\mu\text{M}$	-7.880		
	9.77 $\mu\text{M}$	93.900		
	3.05 $\mu\text{M}$	81.060		
	953.87 $\text{nM}$	22.330		
	298.02 $\text{nM}$	17.300		
	93.13 $\text{nM}$	8.460		
	29.10 $\text{nM}$	-3.530		
	9.09 $\text{nM}$	-4.230		
	2.84 $\text{nM}$	-6.140		

23/146

					
59-0069					
59-0069	100.00 μM	5.490			
	31.25 μM	9.870			
	9.77 μM	18.090			
	3.05 μM	-7.180			
	953.67 nM	-2.840			
	298.02 nM	-3.710			
	93.13 nM	-11.180			
	29.10 nM	-5.790			
	9.09 nM	-7.180			
	2.84 nM	-4.750			
					
59-0070					
59-0070	100.00 μM	-25.930			
	31.25 μM	-23.000			
	9.77 μM	36.060			
	3.05 μM	214.280			
	953.67 nM	158.530			
	298.02 nM	72.890			
	93.13 nM	20.940			
	29.10 nM	7.760			
	9.09 nM	7.590			
	2.84 nM	-8.400			
					
59-0071					
59-0071	100.00 μM	-18.650			
	31.25 μM	-15.540			
	9.77 μM	17.060			
	3.05 μM	176.090			
	953.67 nM	76.070			
	298.02 nM	31.260			
	93.13 nM	16.410			
	29.10 nM	4.870			
	9.09 nM	-7.330			
	2.84 nM	-4.660			

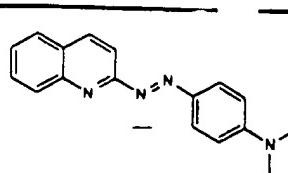
24 / 146

<chem>CSc1ccc(O)cc(C(=O)Nc2nc3ccccc3s2)</chem>				
59-0072				
59-0072	100.00 $\mu$ M	-19.750		
	31.25 $\mu$ M	-18.650		
	9.77 $\mu$ M	-18.430		
	3.05 $\mu$ M	-15.770		
	953.67 nM	9.970		
	298.02 nM	74.740		
	93.13 nM	175.430		
	29.10 nM	213.580		
	9.09 nM	164.320		
	2.84 nM	119.100		
	888.16 pM	60.770		
<chem>CC(F)(F)c1cc(N2CCN(c3cc(F)cc(F)c3)CC2)nc3cc(F)cc(F)c3</chem>				
59-0073				
59-0073	100.00 $\mu$ M	-3.010		
	31.25 $\mu$ M	-4.830		
	9.77 $\mu$ M	-9.860		
	3.05 $\mu$ M	-4.680		
	953.67 nM	-6.500		
	298.02 nM	-2.510		
	93.13 nM	7.140		
	29.10 nM	0.97		
	9.09 nM	-5.5		
	2.84 nM	5.3		
<chem>CC(F)(F)c1cc(Cl)c2c(c1)N(CCC3=CC(F)(F)C(Cl)=CC3)C=C2</chem>				
59-0074				
59-0074	100.00 $\mu$ M	-2.85		
	31.25 $\mu$ M	2.14		
	9.77 $\mu$ M	-4.85		
	3.05 $\mu$ M	-3.5		
	953.67 nM	-4.85		
	298.02 nM	9.95		
	93.13 nM	-4.47		
	29.10 nM	-8		
	9.09 nM	-4.17		
	2.84 nM	6.97		

25 / 146

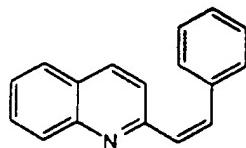
<chem>CN1CC[C@H]2[C@H](C[C@H]1Cc3cc(F)c(F)c(Cl)c3)C(=O)c4ccc(Cl)cc4Cl[C@H]2Cc5cc(F)c(F)c(Cl)c5</chem>					
59-0075					
59-0075	100.00 $\mu$ M	-0.68			
	31.25 $\mu$ M	-10.16			
	9.77 $\mu$ M	-5.35			
	3.05 $\mu$ M	-6.51			
	953.67 nM	-0.88			
	298.02 nM	5.97			
	93.13 nM	0.97			
	29.10 nM	-2.35			
	9.09 nM	0.32			
	2.84 nM	10.47			
<chem>CN1CC[C@H]2[C@H](C[C@H]1Cc3cc(F)c(F)c(Cl)c3)C(=O)c4ccc(Cl)cc4Cl[C@H]2Cc5cc(F)c(O)c(Cl)c5</chem>					
59-0076					
59-0076	100.00 $\mu$ M	-19.12			
	31.25 $\mu$ M	9.29			
	9.77 $\mu$ M	10.63			
	3.05 $\mu$ M	22.43			
	953.67 nM	19.93			
	298.02 nM	3.47			
	93.13 nM	19.93			
	29.10 nM	10.63			
	9.09 nM	14.28			
	2.84 nM	11.3			
<chem>CN1CC[C@H]2[C@H](C[C@H]1Cc3cc(F)c(F)c(Cl)c3)C(=O)c4ccc(Cl)cc4Cl[C@H]2Cc5cc(F)c(F)c(Cl)c5</chem>					
59-0077					
59-0077	100.00 $\mu$ M	-20.96			
	31.25 $\mu$ M	-18.23			
	9.77 $\mu$ M	-10.58			
	3.05 $\mu$ M	-11.96			
	953.67 nM	-19.44			
	298.02 nM	-17.3			
	93.13 nM	-13.79			
	29.10 nM	-15.82			
	9.09 nM	-14.09			
	2.84 nM	-14.4			

26/146



59-0078

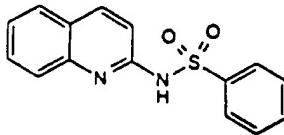
100.00 μM	-26.540
31.25 μM	-22.560
9.77 μM	71.530
3.05 μM	207.960
953.67 nM	379.230
298.02 nM	241.460
93.13 nM	138.100
29.10 nM	84.020
9.09 nM	50.350
2.84 nM	56.500
0.80 nM	92.520



59-0079

59-0079

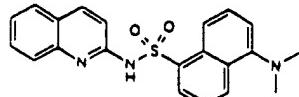
100.00 μM	-34.980
31.25 μM	-21.390
9.77 μM	37.200
3.05 μM	122.580
953.67 nM	69.010
298.02 nM	64.000
93.13 nM	46.490
29.10 nM	30.310
9.09 nM	33.490
2.84 nM	29.760



59-0080

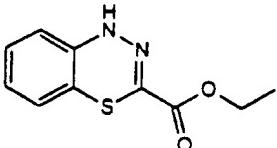
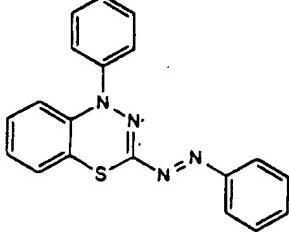
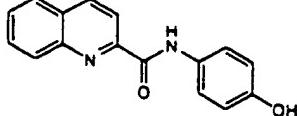
59-0080

100.00 μM	5.390
31.25 μM	5.560
9.77 μM	6.440
3.05 μM	2.440
953.67 nM	-5.030
298.02 nM	7.660
93.13 nM	-3.630
29.10 nM	3.850
9.09 nM	1.050
2.84 nM	6.940

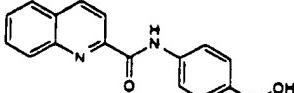
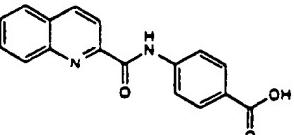
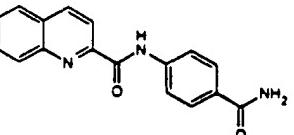


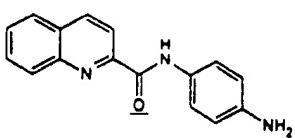
59-0081

27/146

59-0081		100.00 $\mu\text{M}$	62.840
		31.25 $\mu\text{M}$	11.300
		9.77 $\mu\text{M}$	-8.670
		3.05 $\mu\text{M}$	2.440
		953.67 $\text{nM}$	-5.200
		298.02 $\text{nM}$	-2.080
		93.13 $\text{nM}$	1.220
		29.10 $\text{nM}$	-2.250
		9.09 $\text{nM}$	1.050
		2.84 $\text{nM}$	-3.300
			
59-0082		100.00 $\mu\text{M}$	111.79
59-0082		31.25 $\mu\text{M}$	62.68
		9.77 $\mu\text{M}$	32.36
		3.05 $\mu\text{M}$	9.11
		953.67 $\text{nM}$	-10.62
		298.02 $\text{nM}$	-1.86
		93.13 $\text{nM}$	-6.89
		29.10 $\text{nM}$	-3.91
		9.09 $\text{nM}$	2.22
		2.84 $\text{nM}$	16.36
			
59-0083		100.00 $\mu\text{M}$	48.93
59-0083		31.25 $\mu\text{M}$	40.91
		9.77 $\mu\text{M}$	25.85
		3.05 $\mu\text{M}$	17.85
		953.67 $\text{nM}$	8.55
		298.02 $\text{nM}$	3.9
		93.13 $\text{nM}$	2.05
		29.10 $\text{nM}$	7.99
		9.09 $\text{nM}$	-3.91
		2.84 $\text{nM}$	3.35
			
59-0084		100.00 $\mu\text{M}$	-37.670
59-0084		31.25 $\mu\text{M}$	26.050
		9.77 $\mu\text{M}$	9.210
		3.05 $\mu\text{M}$	10.070

28/146

	953.67 nM	21.700
	298.02 nM	5.900
—	93.13 nM	4.870
	29.10 nM	-10.920
	9.09 nM	10.080
	2.84 nM	-2.080
		
59-0085		
59-0085	100.00 μM	17.070
	31.25 μM	41.890
	9.77 μM	18.500
	3.05 μM	20.340
	953.67 nM	22.490
	298.02 nM	8.090
	93.13 nM	11.790
	29.10 nM	1.240
	9.09 nM	-0.760
	2.84 nM	5.940
		
59-0086		
59-0086	100.00 μM	30.750
	31.25 μM	31.190
	9.77 μM	14.790
	3.05 μM	13.500
	953.67 nM	14.080
	298.02 nM	3.940
	93.13 nM	9.370
	29.10 nM	-2.610
	9.09 nM	-5.040
	2.84 nM	1.530
		
59-0087		
59-0087	100.00 μM	10.660
	31.25 μM	11.080
	9.77 μM	3.100
	3.05 μM	-1.320
	953.67 nM	17.070
	298.02 nM	7.950
	93.13 nM	-4.480
	29.10 nM	4.510
	9.09 nM	-0.470
	2.84 nM	9.660



59-0088

59-0088

100.00 μM

31.25 μM

9.77 μM

3.05 μM

953.67 nM

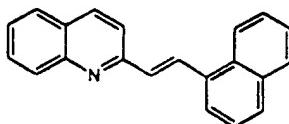
298.02 nM

93.13 nM

29.10 nM

9.09 nM

2.84 nM



59-0089

59-0089

100.00 μM 60.09

31.25 μM 116.25

9.77 μM 65.84

3.05 μM 36.11

953.67 nM 37.98

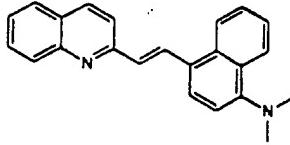
298.02 nM 18.42

93.13 nM 6.33

29.10 nM 13.58

9.09 nM 0.75

2.84 nM -5.77



59-0090

59-0090

100.00 μM 32.77

31.25 μM 24.83

9.77 μM 19.51

3.05 μM 41.31

953.67 nM 9.81

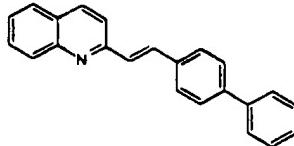
298.02 nM -1.78

93.13 nM 3.53

29.10 nM 2.95

9.09 nM 2.95

2.84 nM 7.81



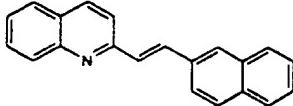
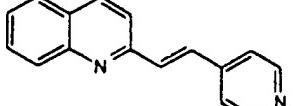
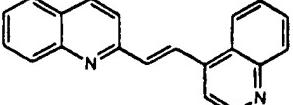
59-0091

59-0091

100.00 μM 0.28

31.25 μM 13.54

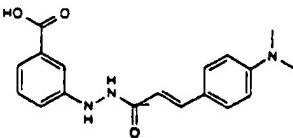
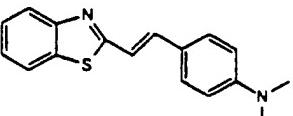
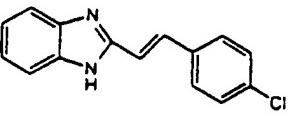
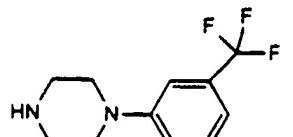
30/146

		9.77  <u>M</u>	95.94
		3.05  <u>M</u>	87.71
		953.67  <u>nM</u>	44.17
		298.02  <u>nM</u>	38.28
		93.13  <u>nM</u>	23.87
		29.10  <u>nM</u>	21.65
		9.09  <u>nM</u>	10.95
		2.84  <u>nM</u>	20.92
			
59-0092			
59-0092		100.00  <u>M</u>	-11.58
		31.25  <u>M</u>	17.84
		9.77  <u>M</u>	50.19
		3.05  <u>M</u>	25.84
		953.67  <u>nM</u>	14.41
		298.02  <u>nM</u>	6.77
		93.13  <u>nM</u>	8.62
		29.10  <u>nM</u>	2.22
		9.09  <u>nM</u>	8.38
		2.84  <u>nM</u>	11
			
59-0093			
59-0093		100.00  <u>M</u>	-11.67
		31.25  <u>M</u>	15.02
		9.77  <u>M</u>	35.44
		3.05  <u>M</u>	29.89
		953.67  <u>nM</u>	22.88
		298.02  <u>nM</u>	19.56
		93.13  <u>nM</u>	5.18
		29.10  <u>nM</u>	7.39
		9.09  <u>nM</u>	4.56
		2.84  <u>nM</u>	5.9
			
59-0094			
59-0094		100.00  <u>M</u>	-17.69
		31.25  <u>M</u>	45.15
		9.77  <u>M</u>	24.97
		3.05  <u>M</u>	19.81
		953.67  <u>nM</u>	9.35
		298.02  <u>nM</u>	1.36
		93.13  <u>nM</u>	9.24
		29.10  <u>nM</u>	-0.48
		9.09  <u>nM</u>	6.16
		2.84  <u>nM</u>	161

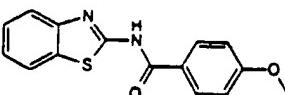
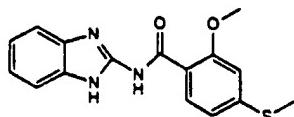
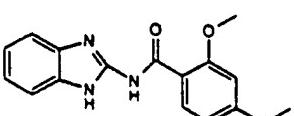
31/146

<chem>O=Cc1ccc(NCc2ccccc2C(=O)Nc3ccc(C)c(N)c3)cc1</chem>					
59-0095					
59-0095	100.00 μM	44.7			
	31.25 μM	47.61			
	9.77 μM	12.78			
	3.05 μM	21.49			
	953.67 nM	15.01			
	298.02 nM	10.22			
	93.13 nM	13.98			
	29.10 nM	20.31			
	9.09 nM	10.9			
	2.84 nM	9.21			
<chem>O=Cc1ccc(NCc2ccccc2C(=O)NCCc3ccc(C)c(N)c3)cc1</chem>					
59-0096					
59-0096	100.00 μM	413.05			
	31.25 μM	287.23			
	9.77 μM	137.38			
	3.05 μM	78.5			
	953.67 nM	49.13			
	298.02 nM	50.68			
	93.13 nM	47.95			
	29.10 nM	26.28			
	9.09 nM	18.75			
	2.84 nM	22.17			
<chem>O=Cc1ccc(NCc2ccccc2C(=O)NCC(=S)Nc3ccc(C)c(N)c3)cc1</chem>					
59-0097					
59-0097	100.00 μM	77.47			
	31.25 μM	201.9			
	9.77 μM	160.93			
	3.05 μM	61.44			
	953.67 nM	47.78			
	298.02 nM	51.54			
	93.13 nM	34.64			
	29.10 nM	43.18			
	9.09 nM	= 39.91			
	2.84 nM	27.13			

32/146

				
59-0098				
59-0098	100.00 μM	-1.38		
	31.25 μM	186.89		
	9.77 μM	221.7		
	3.05 μM	164.69		
	953.67 nM	96.94		
	298.02 nM	68.25		
	93.13 nM	57		
	29.10 nM	51.88		
	9.09 nM	41.29		
	2.84 nM	33.43		
				
59-0099				
59-0099	100.00 μM	13.040		
	31.25 μM	56.880		
	9.77 μM	119.340		
	3.05 μM	237.420		
	953.67 nM	285.440		
	298.02 nM	164.610		
	93.13 nM	123.300		
	29.10 nM	69.240		
	9.09 nM	44.500		
	2.84 nM	47.390		
				
59-0100				
59-0100	100.00 μM	-10.020		
	31.25 μM	-10.730		
	9.77 μM	30.340		
	3.05 μM	114.410		
	953.67 nM	77.540		
	298.02 nM	40.290		
	93.13 nM	35.730		
	29.10 nM	28.290		
	9.09 nM	17.480		
	2.84 nM	11.470		
				
59-0101				
59-0101	100.00 μM	26.370		

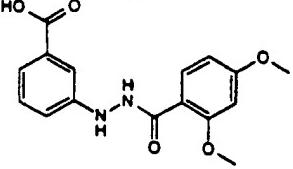
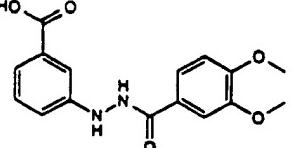
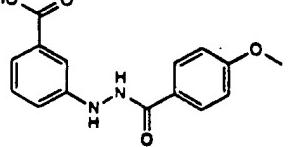
33/146

		31.25 uM	12.440
		9.77 uM	-0.780
		3.05 uM	10.280
		953.67 nM	2.110
		298.02 nM	7.860
		93.13 nM	1.140
		29.10 nM	2.820
		9.09 nM	4.150
		2.84 nM	5.590
			
59-0102	284.34		
59-0102		100.00 uM	-24.350
		31.25 uM	-11.140
		9.77 uM	63.540
		3.05 uM	121.320
		953.67 nM	79.530
		298.02 nM	72.460
		93.13 nM	68.290
		29.10 nM	45.690
		9.09 nM	27.260
		2.84 nM	42.330
		858.18 pM	33.430
			
59-0103	313.38		
		100.00 uM	-29.691
		31.25 uM	-29.531
		9.77 uM	-28.221
		3.05 uM	-27.721
		953.67 nM	-5.581
		298.02 nM	54.151
		93.13 nM	170.951
		29.10 nM	222.871
		9.09 nM	210.391
		2.84 nM	203.41
		0.80 nM	114.551
			
59-0104	297.31		
		100.00 uM	-29.84
		31.25 uM	-26.72
		9.77 uM	-29.21
		3.05 uM	-27.051
		953.67 nM	24.371
		298.02 nM	196.421
		93.13 nM	213.891

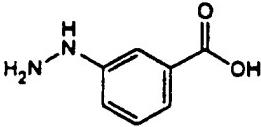
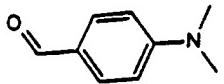
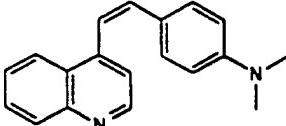
34/146

		29.10 nM	220.04
		9.09 nM	245.42
		2.84 nM	182.45
		0.80 nM	119.55
	59-0105	267.29	
		100.00 uM	-25.72
		31.25 uM	-15.89
		9.77 uM	31.7
		3.05 uM	54.17
		953.67 nM	53.67
		298.02 nM	41.35
		93.13 nM	44.5
		29.10 nM	39.02
		9.09 nM	25.38
		2.84 nM	31.7
		0.80 nM	18.05
	59-0106	297.31	
		100.00 uM	-14.05
		31.25 uM	223.52
		9.77 uM	202.58
		3.05 uM	107.73
		953.67 nM	71.3
		298.02 nM	44.84
		93.13 nM	26.54
		29.10 nM	23.05
		9.09 nM	27.87
		2.84 nM	12.23
		0.80 nM	11.4
	59-0107	332.38	
		100.00 uM	48.55
		31.25 uM	22.87
		9.77 uM	7.19
		3.05 uM	0.85
		953.67 nM	-11.12
		298.02 nM	-3.92
		93.13 nM	1.09
		29.10 nM	-15.69

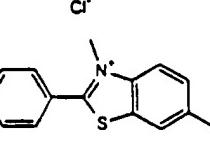
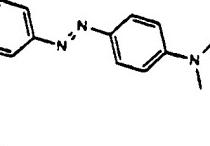
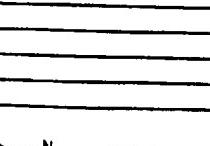
35/146

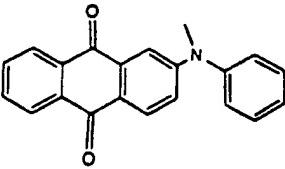
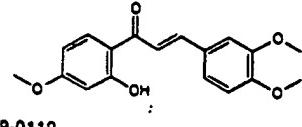
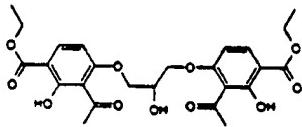
		9.09 nM	11.32
		2.84 nM	-2.62
		0.80 nM	-16.11
	59-0108	316.31	
		100.00 uM	227.73
		31.25 uM	98.02
		9.77 uM	58.57
		3.05 uM	37.23
		953.67 nM	18.94
		298.02 nM	25.88
		93.13 nM	-4.8
		29.10 nM	2.62
		9.09 nM	-4.8
		2.84 nM	3.92
		0.80 nM	4.14
	59-0109	316.31	
		100.00 uM	43.12
		31.25 uM	27.64
		9.77 uM	5.89
		3.05 uM	6.32
		953.67 nM	13.51
		298.02 nM	7.85
		93.13 nM	3.71
		29.10 nM	-3.27
		9.09 nM	5.01
		2.84 nM	-4.58
		0.80 nM	6.98
	59-0110	288.29	
		100.00 uM	65.11
		31.25 uM	67.05
		9.77 uM	-35.27
		3.05 uM	25.26
		953.67 nM	27.01
		298.02 nM	15.24

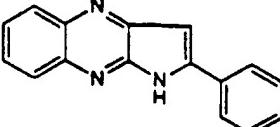
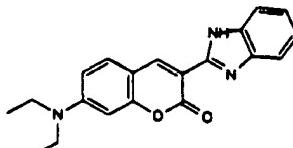
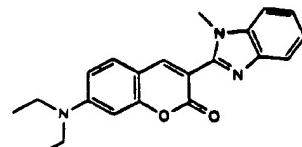
36/146

		93.13 nM	0.68
		29.10 nM	5.89
		9.09 nM	5.45
		2.84 nM	10.24
		0.80 nM	4.14
			
59-0111	152.15	100.00 μM	23.380
		31.25 μM	22.330
		9.77 μM	12.260
		3.05 μM	5.390
		953.67 nM	2.190
		298.02 nM	1.230
		93.13 nM	2.430
		29.10 nM	6.350
		9.09 nM	4.350
		2.84 nM	4.350
		0.80 nM	3.230
			
59-0112	149.19	100.00 μM	2.670
		31.25 μM	4.670
		9.77 μM	2.750
		3.05 μM	3.790
		953.67 nM	4.270
		298.02 nM	1.150
		93.13 nM	9.630
		29.10 nM	0.920
		9.09 nM	0.510
		2.84 nM	12.900
		0.80 nM	2.990
			
59-0113	274.37	100.00 μM	22.010
		31.25 μM	25.940
		9.77 μM	7.500
		3.05 μM	3.070
		953.67 nM	-0.760
		298.02 nM	-4.690
		93.13 nM	-4.790
		29.10 nM	5.090
		9.09 nM	0.150
		2.84 nM	-0.250
		0.80 nM	0.150

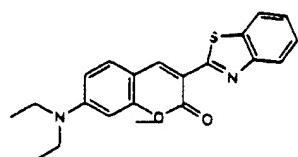
37/146

59-0114	475.54		
	100.00 $\mu\text{M}$	52.030	
	31.25 $\mu\text{M}$	36.120	
	9.77 $\mu\text{M}$	25.840	
	3.05 $\mu\text{M}$	16.670	
	953.67 nM	12.540	
	298.02 nM	9.420	
	93.13 nM	-1.060	
	29.10 nM	2.160	
	9.09 nM	-6.000	
	2.84 nM	2.470	
	0.80 nM	-1.460	
			
59-0115	318.87		
	100.00 $\mu\text{M}$	73.700	
	31.25 $\mu\text{M}$	2.770	
	9.77 $\mu\text{M}$	-10.430	
	3.05 $\mu\text{M}$	-12.340	
	953.67 nM	-13.750	
	298.02 nM	-13.960	
	93.13 nM	-11.940	
	29.10 nM	-0.830	
	9.09 nM	-8.820	
	2.84 nM	-0.950	
	0.80 nM	-0.050	
			
59-0116	269.30		
	100.00 $\mu\text{M}$	31.380	
	31.25 $\mu\text{M}$	109.060	
	9.77 $\mu\text{M}$	231.070	
	3.05 $\mu\text{M}$	240.670	
	953.67 nM	132.020	
	298.02 nM	75.820	
	93.13 nM	53.250	
	29.10 nM	47.500	
	9.09 nM	39.440	
	2.84 nM	42.170	
	0.80 nM	31.180	
			
59-0117	268.38		
	100.00 $\mu\text{M}$	68.520	

		31.25   uM	-7.450
		9.77   uM	111.630
		3.05   uM	64.340
		953.67   nM	4.740
		298.02   nM	-19.270
		93.13   nM	-26.660
		29.10   nM	-26.880
		9.09   nM	-42.180
		2.84   nM	-41.300
		0.80   nM	-39.220
			
59-0118	313.38		
		100.00   uM	-87.170
		31.25   uM	-56.580
		9.77   uM	-58.060
		3.05   uM	-55.720
		953.67   nM	-48.200
		298.02   nM	-50.300
		93.13   nM	-33.310
		29.10   nM	-47.340
		9.09   nM	-49.310
		2.84   nM	-56.200
		0.80   nM	-57.310
			
59-0119	314.34		
		100.00   uM	167.500
		31.25   uM	-29.240
		9.77   uM	-57.800
		3.05   uM	-52.030
		953.67   nM	-54.240
		298.02   nM	-53.870
		93.13   nM	-38.110
		29.10   nM	-55.100
		9.09   nM	-52.270
		2.84   nM	-53.500
		0.80   nM	-43.650
			
59-0120	504.49		
		100.00   uM	-82.780
		31.25   uM	-80.470
		9.77   uM	-88.800
		3.05   uM	-80.790
		953.67   nM	-54.240
		298.02   nM	-45.250
		93.13   nM	-50.680

		29.10 nM	-50.300
		9.09 nM	-50.300
		2.84 nM	-50.300
		0.80 nM	-43.280
			
59-0121	245.29		
		100.00 μM	-79.690
		31.25 μM	-75.590
		9.77 μM	25.850
		3.05 μM	94.650
		953.67 nM	43.910
		298.02 nM	-1.800
		93.13 nM	-4.150
		29.10 nM	-22.050
		9.09 nM	-31.110
		2.84 nM	-26.760
		0.80 nM	-28.270
			
59-0122	333.39		
		100.00 μM	-19.050
		31.25 μM	-12.080
		9.77 μM	-7.610
		3.05 μM	25.210
		953.67 nM	83.580
		298.02 nM	87.220
		93.13 nM	63.890
		29.10 nM	42.680
		9.09 nM	45.320
		2.84 nM	37.780
		0.80 nM	27.030
			
59-0123	347.42		
		100.00 μM	34.430
		31.25 μM	34.710
		9.77 μM	38.620
		3.05 μM	55.100
		953.67 nM	51.900
		298.02 nM	41.410
		93.13 nM	29.970
		29.10 nM	-13.760
		9.09 nM	17.120
		2.84 nM	13.480
		0.80 nM	1.190

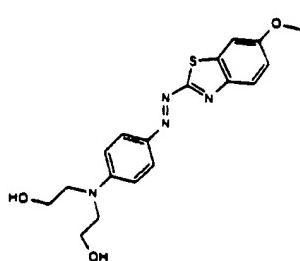
40/146



59-0124

350.44

	100.00 $\mu\text{M}$	56.840
	31.25 $\mu\text{M}$	61.500
	9.77 $\mu\text{M}$	145.880
	3.05 $\mu\text{M}$	135.830
	953.67 $\text{nM}$	268.990
	298.02 $\text{nM}$	224.290
	93.13 $\text{nM}$	134.850
	29.10 $\text{nM}$	91.890
	9.09 $\text{nM}$	80.390
	2.84 $\text{nM}$	63.060
	0.80 $\text{nM}$	51.460

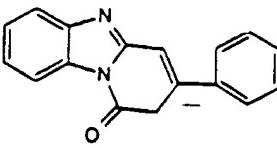
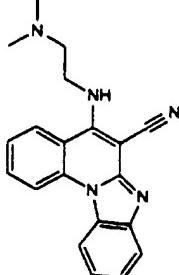
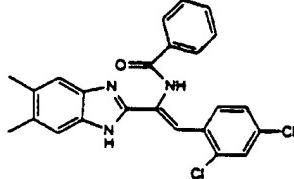


59-0125

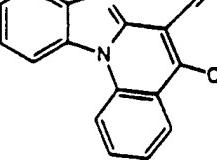
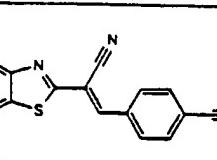
372.45

	100.00 $\mu\text{M}$	-6.780
	31.25 $\mu\text{M}$	67.530
	9.77 $\mu\text{M}$	54.120
	3.05 $\mu\text{M}$	28.700
	953.67 $\text{nM}$	21.580
	298.02 $\text{nM}$	22.280
	93.13 $\text{nM}$	22.700
	29.10 $\text{nM}$	1.630
	9.09 $\text{nM}$	15.700
	2.84 $\text{nM}$	9.840
	0.80 $\text{nM}$	8.460

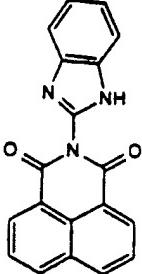
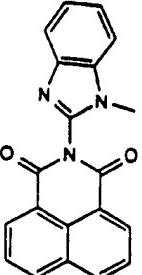
41 / 146

					
59-0126	260.30				
	100.00 μM	-17.390			
	31.25 μM	-13.100			
	9.77 μM	9.270			
	3.05 μM	40.530			
	953.67 nM	21.390			
	298.02 nM	25.660			
	93.13 nM	9.430			
	29.10 nM	6.360			
	9.09 nM	6.510			
	2.84 nM	0.080			
	0.80 nM	3.750			
					
59-0127	329.41				
	100.00 μM	-20.610			
	31.25 μM	-21.820			
	9.77 μM	-6.060			
	3.05 μM	-3.900			
	953.67 nM	-8.820			
	298.02 nM	-6.200			
	93.13 nM	11.880			
	29.10 nM	1.610			
	9.09 nM	3.600			
	2.84 nM	-2.070			
	0.80 nM	4.220			
					
59-0128	436.34				
	100.00 μM				
	31.25 μM				
	9.77 μM				
	3.05 μM				
	953.67 nM				
	298.02 nM				
	93.13 nM				
	29.10 nM				

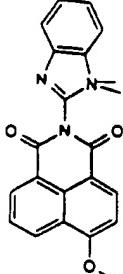
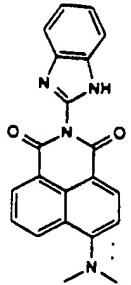
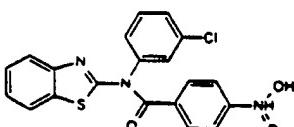
42 / 146

		$K_{dR}$ nM	
		2.84 nM	
		0.80 nM	
			
59-0129	277.71		
		100.00 $\mu$ M	-20.48
		31.25 $\mu$ M	-21.21
		9.77 $\mu$ M	44.38
		3.05 $\mu$ M	4.38
		953.67 nM	5.9
		298.02 nM	3.6
		93.13 nM	2.07
		29.10 nM	4.22
		9.09 nM	-0.68
		2.84 nM	12.48
		0.80 nM	-0.53
			
59-0130	287.34		
		100.00 $\mu$ M	4.38
		31.25 $\mu$ M	8.35
		9.77 $\mu$ M	5.91
		3.05 $\mu$ M	4.98
		953.67 nM	0.39
		298.02 nM	8.66
		93.13 nM	2.85
		29.10 nM	3.6
		9.09 nM	4.36
		2.84 nM	8.96
		0.80 nM	24.75
			
59-0131	331.22		
		100.00 $\mu$ M	8.75
		31.25 $\mu$ M	0.12
		9.77 $\mu$ M	-10.38
		3.05 $\mu$ M	-8.39
		953.67 nM	-2.81
		298.02 nM	1.61
		93.13 nM	-1.98
		29.10 nM	-2.59
		9.09 nM	0.14
		2.84 nM	-5.77

43/146

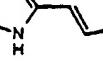
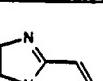
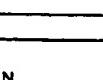
		0.80 nM	-0.51		
					
59-0132	313.32				
		100.00 μM	-17.11		
		31.25 μM	-14.81		
		9.77 μM	-14.37		
		3.05 μM	-12.92		
		953.67 nM	-13.54		
		298.02 nM	-10.38		
		93.13 nM	-3.65		
		29.10 nM	-7.66		
		9.09 nM	-6.18		
		2.84 nM	-9.97		
		0.80 nM	-2.81		
					
59-0133	327.34				
		100.00 μM	-16.04		
		31.25 μM	-16.91		
		9.77 μM	-17.31		
		3.05 μM	-16.71		
		953.67 nM	-9.34		
		298.02 nM	-12.69		
		93.13 nM	-11.23		
		29.10 nM	-17.74		
		9.09 nM	6.02		
		2.84 nM	-4.71		
		0.80 nM	0.55		

44/146

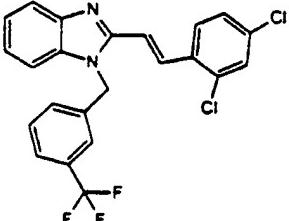
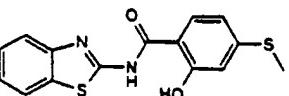
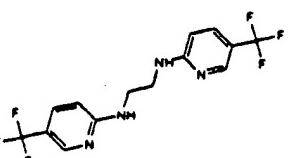
				
59-0134	357.37			
	100.00 $\mu$ M			
	31.25 $\mu$ M			
	9.77 $\mu$ M			
	3.05 $\mu$ M			
	953.67 nM			
	298.02 nM			
	93.13 nM			
	29.10 nM			
	9.09 nM			
	2.84 nM			
	0.80 nM			
				
59-0135	358.39			
	100.00 $\mu$ M	-21.3		
	31.25 $\mu$ M	-14.16		
	9.77 $\mu$ M	-1.98		
	3.05 $\mu$ M	0.97		
	953.67 nM	11.68		
	298.02 nM	-1.13		
	93.13 nM	-1.55		
	29.10 nM	-2.81		
	9.09 nM	12.11		
	2.84 nM	-5.75		
	0.80 nM	4.54		
				
59-0136	411.87			
	100.00 $\mu$ M			
	31.25 $\mu$ M	+		
	9.77 $\mu$ M			
	3.05 $\mu$ M			
	953.67 nM			



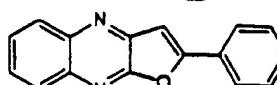
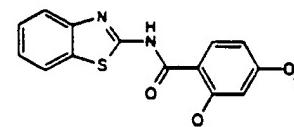
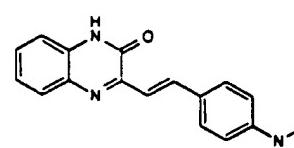
46 / 146

		29.10 nM	14.91
		9.09 nM	13.93
		2.84 nM	18.61
		0.80 nM	10.05
	59-0140	289.17	
		100.00 μM	
		31.25 μM	
		9.77 μM	
		3.05 μM	
		953.67 nM	
		298.02 nM	
		93.13 nM	
		29.10 nM	
		9.09 nM	
		2.84 nM	
		0.80 nM	
	59-0141	437.33	
		100.00 μM	-6.76
		31.25 μM	5.69
		9.77 μM	19.85
		3.05 μM	43.96
		953.67 nM	44.73
		298.02 nM	37.12
		93.13 nM	24.36
		29.10 nM	18.61
		9.09 nM	26.71
		2.84 nM	15.96
		0.80 nM	7.87
	59-0142	379.29	
		100.00 μM	9.43
		31.25 μM	33.72
		9.77 μM	47.33
		3.05 μM	40.18
		953.67 nM	36.53
		298.02 nM	29.94
		93.13 nM	22.11

47/146

	$\text{IC}_{50} \text{nM}$	$\text{ED}_{50} \text{nM}$
	0.09 nM	19.14
	2.84 nM	10.38
	0.80 nM	17.12
		
59-0143	447.29	
	100.00 $\mu\text{M}$	0.41
	31.25 $\mu\text{M}$	34.39
	9.77 $\mu\text{M}$	42.21
	3.05 $\mu\text{M}$	50.57
	953.67 nM	36.94
	298.02 nM	27.23
	93.13 nM	16.99
	29.10 nM	19.27
	9.09 nM	14.42
	2.84 nM	11.33
	0.80 nM	23.72
		
59-0144	316.40	
	100.00 $\mu\text{M}$	-14.59
	31.25 $\mu\text{M}$	-4.44
	9.77 $\mu\text{M}$	47.11
	3.05 $\mu\text{M}$	53.89
	953.67 nM	43.11
	298.02 nM	29.21
	93.13 nM	18.51
	29.10 nM	12.91
	9.09 nM	5.54
	2.84 nM	3.71
	0.80 nM	5.87
		
59-0145	350.27	
	100.00 $\mu\text{M}$	435.91
	31.25 $\mu\text{M}$	422.15
	9.77 $\mu\text{M}$	446.93
	3.05 $\mu\text{M}$	434.17
	953.67 nM	238.34
	298.02 nM	45.99
	93.13 nM	9.22
	29.10 nM	7.71
	9.09 nM	0.11

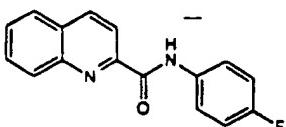
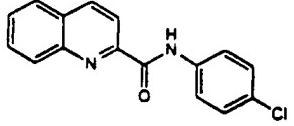
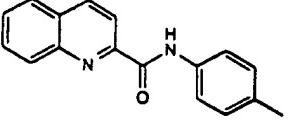
48/146

		2.84 nM	6.27
		0.80 nM	3.55
	59-0146	246.27	
		100.00 uM	-63.05
		31.25 uM	4.42
		9.77 uM	-13.73
		3.05 uM	-16.45
		953.67 nM	-35.47
		298.02 nM	-51.25
		93.13 nM	-50.13
		29.10 nM	-42.92
		9.09 nM	-45.84
		2.84 nM	-56.58
		0.80 nM	-39.66
	59-0147	314.36	
		100.00 uM	-85
		31.25 uM	-85
		9.77 uM	-80.29
		3.05 uM	-41.87
		953.67 nM	78.69
		298.02 nM	269.13
		93.13 nM	323.59
		29.10 nM	339.88
		9.09 nM	270.48
		2.84 nM	245.58
		0.80 nM	180.33
	59-0148	291.35	
		100.00 uM	-68.38
		31.25 uM	-38.33
		9.77 uM	-2.3
		3.05 uM	12.12
		953.67 nM	-2.42
		298.02 nM	-16.21
		93.13 nM	-30.87
		29.10 nM	-35.58
		9.09 nM	-39.07
		2.84 nM	-41.18
		0.80 nM	-45.53

49 / 146

59-0149	329.33				
	100.00 μM	-16.9			
	31.25 μM	-1.8			
	9.77 μM	-0.53			
	3.05 μM	15.29			
	953.67 nM	78.78			
	298.02 nM	163.5			
	93.13 nM	223.57			
	29.10 nM	173.93			
	9.09 nM	122.3			
	2.84 nM	98.02			
	0.80 nM	69.06			
59-0150	304.39				
	100.00 μM	63.32			
	31.25 μM	193.53			
	9.77 μM	419.26			
	3.05 μM	497.21			
	953.67 nM	295.19			
	298.02 nM	193.35			
	93.13 nM	99.46			
	29.10 nM	69.96			
	9.09 nM	59			
	2.84 nM	52.16			
	0.80 nM	48.75			
59-0151	278.311				
59-0151	100.00 μM	-6.660			
	31.25 μM	18.240			
	9.77 μM	18.300			
	3.05 μM	11.690			
	953.67 nM	8.500			
	298.02 nM	9.070			
	93.13 nM	8.110			
	29.10 nM	5.880			
	9.09 nM	7.700			
	2.84 nM	2.000			
	0.80 nM	1.210			

50/146

	59-0152	266.275					
	59-0152		100.00 μM	-6.890			
			31.25 μM	12.480			
			9.77 μM	21.950			
			3.05 μM	12.820			
			953.67 nM	7.350			
			298.02 nM	4.280			
			93.13 nM	9.750			
			29.10 nM	4.860			
			9.09 nM	1.320			
			2.84 nM	4.280			
			0.80 nM	4.160			
	59-0153	282.73					
	59-0153		100.00 μM	-4.150			
			31.25 μM	-0.390			
			9.77 μM	11.120			
			3.05 μM	14.540			
			953.67 nM	9.520			
			298.02 nM	11.570			
			93.13 nM	-0.160			
			29.10 nM	1.550			
			9.09 nM	-0.860			
			2.84 nM	4.730			
			0.80 nM	5.650			
	59-0154	262.312					
	59-0154		100.00 μM	0.290			
			31.25 μM	24.670			
			9.77 μM	15.680			
			3.05 μM	14.540			
			953.67 nM	13.170			
			298.02 nM	5.540			
			93.13 nM	2.690			
			29.10 nM	-1.190			
			9.09 nM	2.460			
			2.84 nM	4.170			
			0.80 nM	1.890			

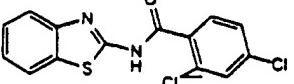
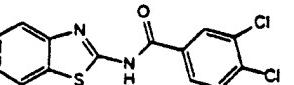
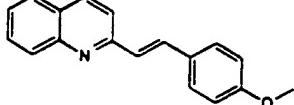
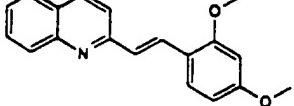
51/146

59-0155	316.282				
59-0155	100.00 $\mu$ M	-2.950			
	31.25 $\mu$ M	1.000			
	9.77 $\mu$ M	-9.450			
	3.05 $\mu$ M	-0.220			
	953.67 nM	0.690			
	298.02 nM	5.090			
	93.13 nM	-3.250			
	29.10 nM	0.530			
	9.09 nM	-1.900			
	2.84 nM	9.480			
	0.80 nM	-1.130			
59-0156	333.391				
59-0156	100.00 $\mu$ M	5.840			
	31.25 $\mu$ M	2.050			
	9.77 $\mu$ M	7.980			
	3.05 $\mu$ M	6.690			
	953.67 nM	-0.370			
	298.02 nM	-1.680			
	93.13 nM	-3.550			
	29.10 nM	-7.340			
	9.09 nM	-1.590			
	2.84 nM	2.650			
	0.80 nM	2.500			
59-0157	290.366				
59-0157	100.00 $\mu$ M	-6.440			
	31.25 $\mu$ M	14.920			
	9.77 $\mu$ M	19.930			
	3.05 $\mu$ M	11.440			
	953.67 nM	6.570			
	298.02 nM	-7.190			
	93.13 nM	0.080			
	29.10 nM	-0.230			
	9.09 nM	-4.460			
	2.84 nM	2.200			
	0.80 nM	9.920			

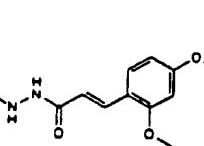
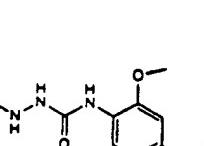
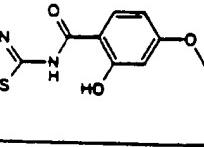
52/146

59-0158	308.337					
59-0158		100.00 μM	-5.980			
		31.25 μM	3.720			
		9.77 μM	16.140			
		3.05 μM	27.080			
		953.67 nM	9.930			
		298.02 nM	11.900			
		93.13 nM	2.810			
		29.10 nM	3.110			
		9.09 nM	0.690			
		2.84 nM	1.900			
		0.80 nM	7.970			
59-0159	308.337					
59-0159		100.00 μM	2.790			
		31.25 μM	13.530			
		9.77 μM	4.700			
		3.05 μM	10.910			
		953.67 nM	2.800			
		298.02 nM	9.710			
		93.13 nM	4.830			
		29.10 nM	0.650			
		9.09 nM	5.900			
		2.84 nM	6.610			
		0.80 nM	6.250			
59-0160	319.408					
59-0160		100.00 μM	-5.060			
		31.25 μM	-3.390			
		9.77 μM	5.300			
		3.05 μM	15.910			
		953.67 nM	6.610			
		298.02 nM	11.380			
		93.13 nM	4.460			
		29.10 nM	3.520			
		9.09 nM	4.700			
		2.84 nM	-0.650			
		0.80 nM	7.560			

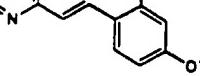
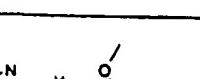
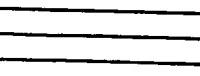
53 / 146

					
59-0196	323.201				
59-0196		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0197	323.201				
59-0197		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0198	261.324				
59-0198		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0199	291.35				
59-0199		100.00 μM			
		31.25 μM			

54 / 146

		IC50 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0200		342.351				
59-0200		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0201		331.328				
59-0201		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0202		300.336				
59-0202		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				

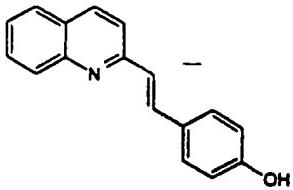
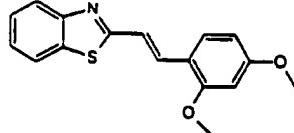
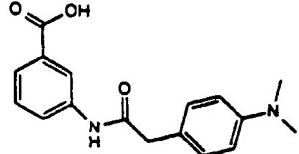
55 /146

			9.09 nM		
			2.84 nM		
			0.80 nM		
					
59-0203		292.338			
59-0203			100.00 μM		
			31.25 μM		
			9.77 μM		
			3.05 μM		
			953.67 nM		
			298.02 nM		
			93.13 nM		
			29.10 nM		
			9.09 nM		
			2.84 nM		
			0.80 nM		
					
59-0204		344.389			
59-0204			100.00 μM		
			31.25 μM		
			9.77 μM		
			3.05 μM		
			953.67 nM		
			298.02 nM		
			93.13 nM		
			29.10 nM		
			9.09 nM		
			2.84 nM		
			0.80 nM		
					
59-0205		318.782			
59-0205			100.00 μM		
			31.25 μM		
			9.77 μM		
			3.05 μM		
			953.67 nM		
			298.02 nM		
			93.13 nM		
			29.10 nM		
			9.09 nM	±	
			2.84 nM		
			0.80 nM		

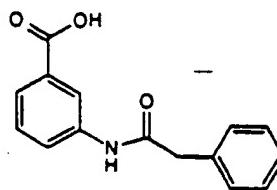
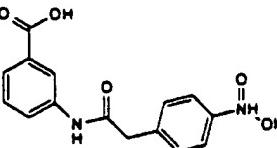
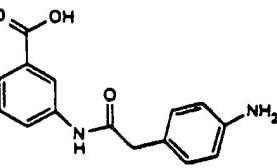
56 / 146

59-0206	348.808					
59-0206		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
59-0207	348.808					
59-0207		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
59-0208	338.307					
59-0208		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

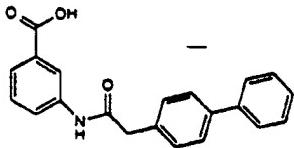
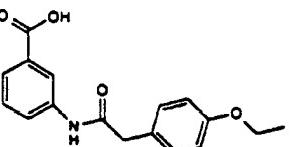
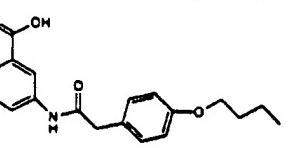
57/146

						
59-0209	247.297					
59-0209		100.00   μM				
		31.25   μM				
		9.77   μM				
		3.05   μM				
		953.67   nM				
		298.02   nM				
		93.13   nM				
		29.10   nM				
		9.09   nM				
		2.84   nM				
		0.80   nM				
						
59-0210	297.376					
59-0210		100.00   μM				
		31.25   μM				
		9.77   μM				
		3.05   μM				
		953.67   nM				
		298.02   nM				
		93.13   nM				
		29.10   nM				
		9.09   nM				
		2.84   nM				
		0.80   nM				
						
59-8000	298.342					
59-8000		100.00   μM				
		31.25   μM				
		9.77   μM				
		3.05   μM				
		953.67   nM				
		298.02   nM				
		93.13   nM				
		29.10   nM				
		9.09   nM		—		
		2.84   nM		1	1	
		0.80   nM				

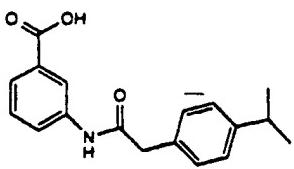
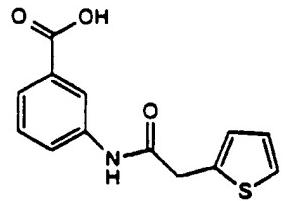
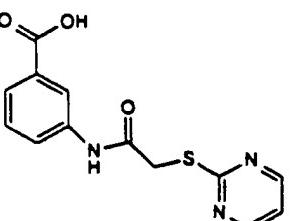
58/146

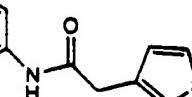
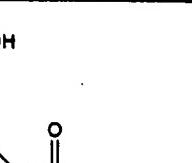
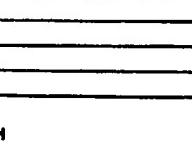
	255.273					
59-8001		100.00 $\mu$ M				
59-8001		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
	302.288					
59-8002		100.00 $\mu$ M				
59-8002		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
	270.288					
59-8003		100.00 $\mu$ M				
59-8003		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

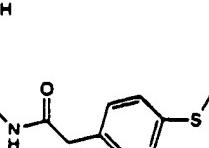
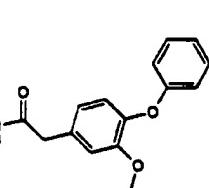
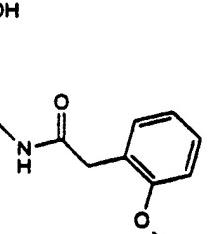
59 / 146

						
59-8004	331.371					
59-8004		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8005	299.326					
59-8005		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8006	327.38					
59-8006		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

60/146

				
59-8007	297.354			
59-8007		100.00 μM		
		31.25 μM		
		9.77 μM		
		3.05 μM		
		953.67 nM		
		298.02 nM		
		93.13 nM		
		29.10 nM		
		9.09 nM		
		2.84 nM		
		0.80 nM		
				
59-8008	261.299			
59-8008		100.00 μM		
		31.25 μM		
		9.77 μM		
		3.05 μM		
		953.67 nM		
		298.02 nM		
		93.13 nM		
		29.10 nM		
		9.09 nM		
		2.84 nM		
		0.80 nM		
				
59-8009	289.313			
59-8009		100.00 μM		
		31.25 μM		
		9.77 μM		
		3.05 μM		
		953.67 nM		
		298.02 nM		
		93.13 nM		
		29.10 nM		
		9.09 nM		

		.IC50 nM	0.80 nM					
								
59-8010		261.299						
59-8010			100.00 uM					
			31.25 uM					
			9.77 uM					
			3.05 uM					
			953.67 nM					
			298.02 nM					
			93.13 nM					
			29.10 nM					
			9.09 nM					
			2.84 nM					
			0.80 nM					
								
59-8011		285.299						
59-8011			100.00 uM					
			31.25 uM					
			9.77 uM					
			3.05 uM					
			953.67 nM					
			298.02 nM					
			93.13 nM					
			29.10 nM					
			9.09 nM					
			2.84 nM					
			0.80 nM					
								
59-8012		294.285						
59-8012			100.00 uM					
			31.25 uM					
			9.77 uM					
			3.05 uM					
			953.67 nM					
			298.02 nM					

		SXLS nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
		
59-8013	301.384	
59-8013		100.00 uM
		31.25 uM
		9.77 uM
		3.05 uM
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
		
59-8014	377.396	
59-8014		100.00 uM
		31.25 uM
		9.77 uM
		3.05 uM
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
		
59-8015	285.299	
59-8015		100.00 uM
		31.25 uM
		9.77 uM
		3.05 uM

63/146

		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
59-8016		285.299			
59-8016		100.00 uM			
		31.25 uM			
		9.77 uM			
		3.05 uM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			

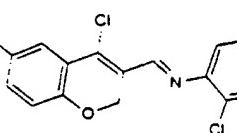
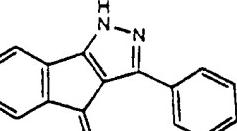
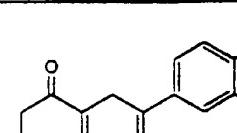
64 / 146

CHEMISTRY	Concentration		ABA-S
51-2229			
51-2229	100.00	uM	125.320
	10.00		28.260
	210.236	2.00	20.140
		0.40	-9.740
		0.08	-9.710
92-3052			
92-3052	131.056	uM	-9.28
	13.106		113.80
	381.516	2.621	12.61
		0.524	20.25
		0.105	24.45
92-3390			
92-3390	145.012	uM	-9.05
	14.501		31.57
	344.798	2.900	139.88
		0.580	49.82
		0.116	21.01
92-3652			
92-3652	214.326	uM	108.15

Figure 4

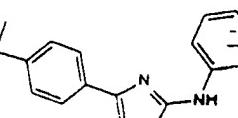
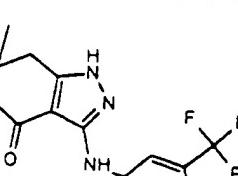
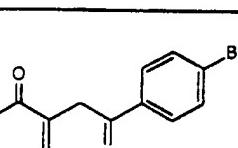
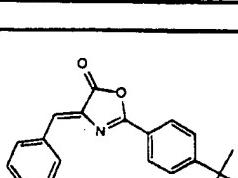
4-L

65 / 146

		21.433
	233.289	4.287
		0.857
		0.171
		
92-6353		
92-6353	155.199	uM
	31.040	
	322.166	15.520
		3.104
		1.552
		0.310
		
92-8007		
92-8007	181.813	uM
	36.323	
	275.311	18.161
		3.632
		1.816
		0.363
		
92-8215		
92-8215	165.123	uM
	33.025	
	302.805	18.512
		3.302
		1.851
		0.330

	69.74
	31.59
	39.70
	18.29
	204.14
	154.94
	28.09
	3.53
	-18.65
	58.65
	142.33
	45.65
	4.47
	32.90
	151.08
	132.29
	59.90
	23.34

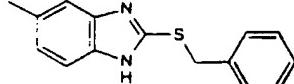
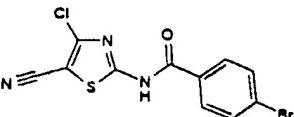
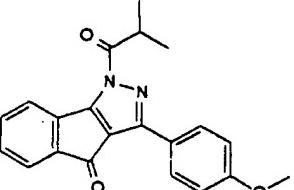
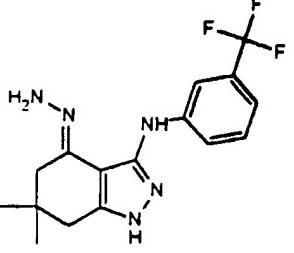
66 / 146

		
92-8258		
92-8258	162.102	uM
	32.420	
	308.447	16.210
		3.242
		1.621
		0.324
		-16.65
		157.44
		101.04
		39.02
		12.78
		
92-8362		
92-8362	154.647	uM
	30.929	
	323.318	15.465
		3.083
		1.546
		0.309
		138.79
		137.00
		65.02
		17.34
		0.41
		
92-8372		
92-8372	150.046	uM
	30.009	
	333.234	15.004
		3.001
		1.500
		0.300
		63.78
		134.71
		92.08
		31.35
		13.20
		
92-9183		

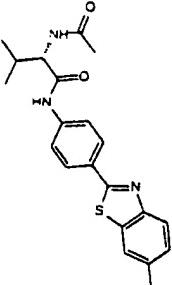
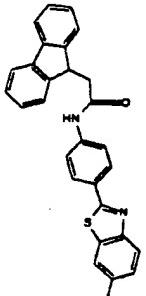
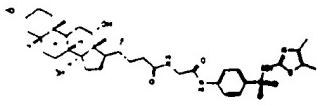
67 / 146

92-9183		137.568	uM	-22.80
		13.757		16.61
	363.457	2.751		101.96
		1.376		
		0.550		58.17
		0.110		38.47
93-0215				
93-0215		182.957	uM	115.230
		18.296		88.110
	273.288	3.659		20.870
		0.732		-28.680
		0.146		5.250
93-0399				
93-0399		131.491	uM	128.130
		13.149		38.560
	380.253	2.630		41.240
		0.526		-4.910
		0.105		3.910
93-0587				
93-0587		222.953	uM	178.130
		22.295		60.410
	224.263	4.459		-0.180
		0.882		-3.470
		0.178		-8.460
93-1327				
93-1327		119.764	uM	-42.000
		11.976		119.130
	417.487	2.385		67.930
		0.479		8.520

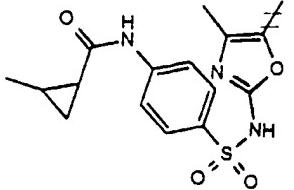
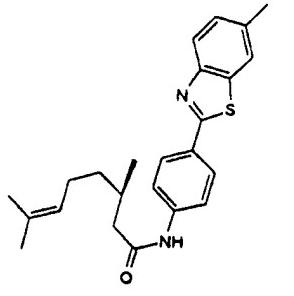
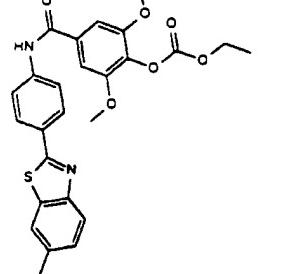
68/146

	0.096	
93-1340		
93-1340	196.576	μM
	19.658	
	254.365	3.932
	0.786	
	0.157	
		
93-1474		
93-1474	145.940	μM
	14.594	
	342.607	2.919
	0.584	
	0.117	
		
93-1766		
93-1766	144.348	μM
	14.435	
	346.386	2.887
	0.577	
	0.115	
		
93-1866		
93-1866	148.214	μM
	14.821	
	75.940	
	173.150	
	14.870	
	-31.290	
	127.340	
	35.710	
	37.630	
	7.280	

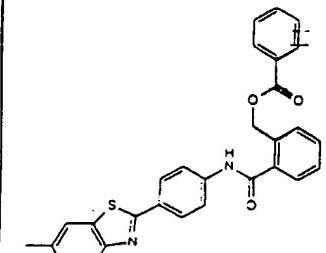
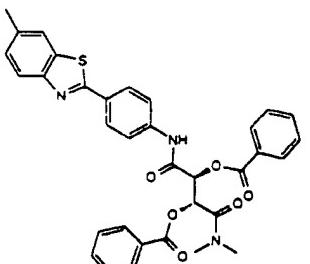
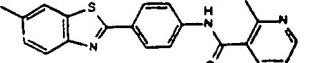
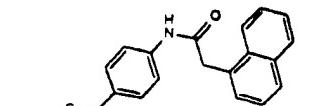
69 / 146

	337.349	2.964	
	--	0.593	
		0.119	
			2.600
			-7.350
			-25.160
			
850-7377			
850-7377		131.062 uM	
		13.106	
	381.498	2.621	
		0.524	
		0.105	
			
850-7413			
850-7413		111.964 uM	
		11.196	
	446.572	2.239	
		0.448	
		0.080	
			
850-7449			
850-7449		69.938 uM	
		6.994	
	714.923	1.399	
		0.280	
		0.056	

70/146

		
850-7485		
850-7485	143.099 uM	
	14.310	
349.409	2.862	
	0.572	
	0.114	
	-42.91	
	28.36	
	153.04	
	74.27	
	50.28	
		
850-7991		
850-7991	127.367 uM	
	12.737	
392.565	2.547	
	0.509	
	0.102	
	-16.87	
	8.95	
	105.51	
	47.53	
	54.26	
		
850-8170		
850-8170	101.513 uM	
	10.151	
462.55	2.030	
	0.406	
	0.081	
	-33.79	
	158.65	
	128.27	
	43.05	
	50.00	

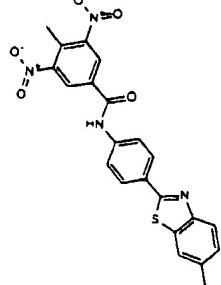
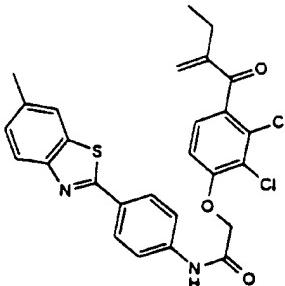
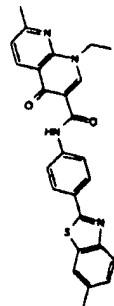
71 / 146

			
850-8205			
850-8205	104.478	uM	
	10.448		
	478.57		
	2.090		
	0.418		
	0.064		
CHIRAL			
			
850-8241			
850-8241	82.279	uM	
	8.228		
	607.695		
	1.846		
	0.329		
	0.088		
			
850-8278			
850-8278	139.101	uM	
	13.910		
	359.451		
	2.782		
	0.556		
	0.111		
			
850-8387			

72 / 146

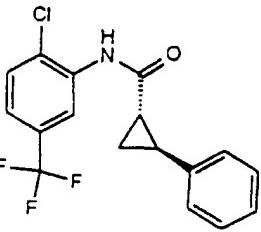
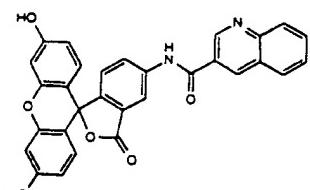
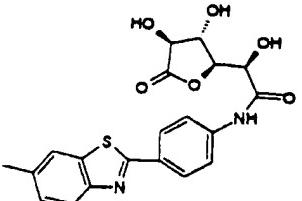
850-8387	122.392	uM
	12.239	
708.523	2.448	
	0.490	
	0.098	
850-8459		
850-8459	87.921	uM
	8.792	
568.692	1.758	
	0.352	
	0.070	
850-8613		
850-8613	151.319	uM
	15.132	
330.428	3.026	
	0.605	
	0.121	
850-8637		
850-8637	85.518	uM
	8.552	
584.673	1.710	
	0.342	
	0.088	

73 / 146

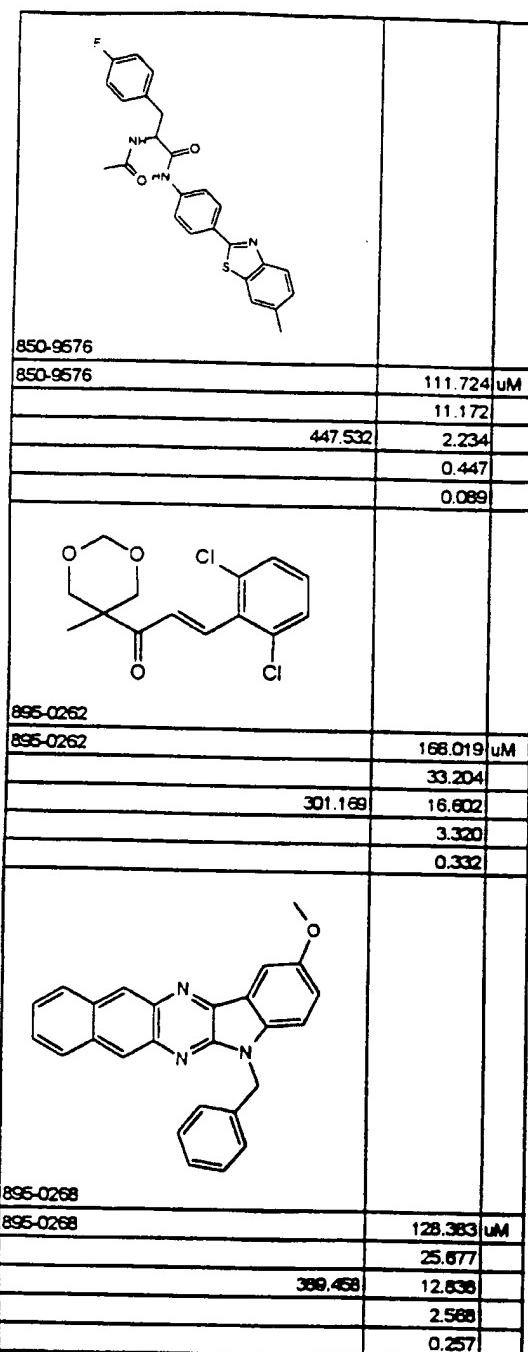
			
850-8889			
	111.493 uM		
	11.149		
	448.467	2.230	
		0.446	
		0.089	
			
850-8964			
	95.156 uM		
	9.516		
	525.464	1.903	
		0.381	
		0.078	
			
850-9071			
	109.998 uM		
	11.000		
	454.562	2.200	
		0.440	

74 / 146

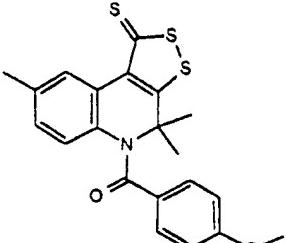
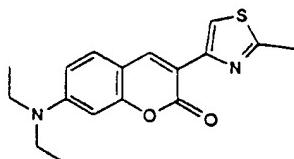
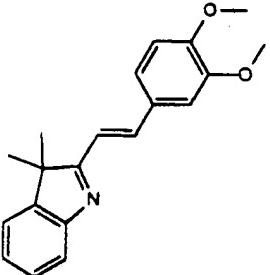
75/146

			
850-9287			
850-9287	147.170 uM		
	14.717		
	339.744	2.943	
		0.589	
		0.118	
			-15.82
			15.82
			130.71
			91.11
			69.05
			
850-9356			
850-9356	99.506 uM		
	9.951		
	502.482	1.990	
		0.398	
		0.080	
			-24.650
			83.140
			168.810
			45.470
			9.740
			
850-9467			
850-9467	120.646 uM		
	12.065		
	414.436	2.413	
		0.483	
		0.097	
			-19.800
			112.990
			122.730
			43.520
			33.140

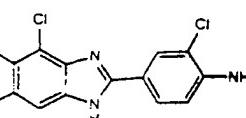
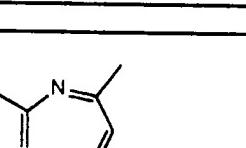
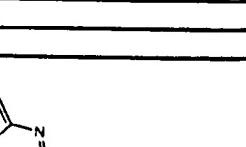
76 / 146



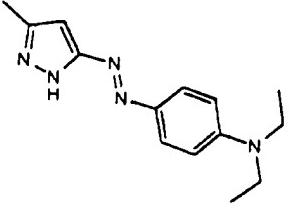
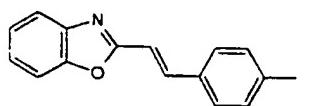
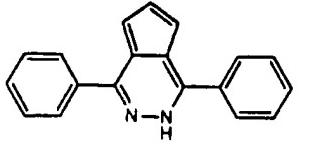
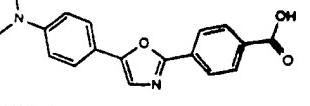
77 / 146

			
895-0594			
895-0594	120.896 uM		
	12.090		
	413.58	2.418	
		0.484	
		0.097	
			-21.63
			25.89
			122.10
			75.32
			39.42
			
895-0857			
895-0857	159.028 uM		
	15.803		
	314.407	3.181	
		0.636	
		0.127	
			-30.48
			148.74
			74.54
			25.82
			3.68
			
895-0984			
895-0984	182.655 uM		
	16.265		
	307.393	3.253	
		0.651	
		0.130	
			-31.08
			325.08
			87.51
			40.39
			16.03

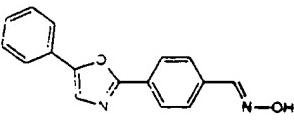
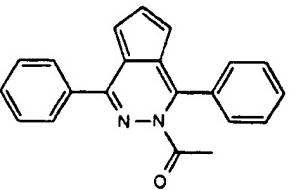
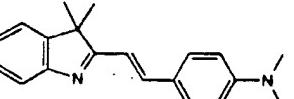
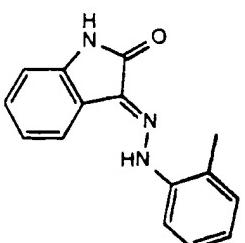
78/146

		
895-1161		
895-1161	152.625	µM
	15.263	
327.602	3.053	
	0.611	
	0.122	
	-5.51	
	109.31	
	56.06	
	29.49	
	24.71	
		
895-1420		
895-1420	220.965	µM
	22.097	
226.279	4.419	
	0.884	
	0.177	
	-19.47	
	110.90	
	49.94	
	33.65	
	20.06	
		
895-1679		
895-1679	180.910	µM
	18.091	
276.383	3.618	
	0.724	
	0.145	
	-30.38	
	111.72	
	102.83	
	18.01	
	0.44	
		
895-1691		
895-1691	182.922	µM
	18.292	
273.34	3.658	
	-16.29	
	50.84	
	105.70	

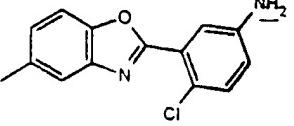
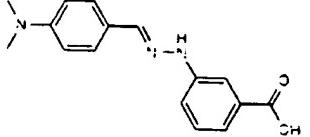
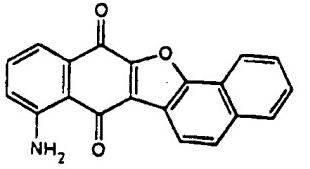
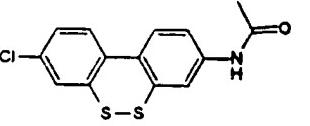
79 / 146

		0.732	
		0.146	
	895-1754		
	895-1754	194.295 uM	
		19.430	
		257.341	3.886
			0.777
			0.155
	895-1888		
	895-1888	212.504 uM	
		21.250	
		235.286	4.250
			0.850
			0.170
	895-2474		
	895-2474	184.952 uM	
		18.485	
		270.335	3.609
			0.740
			0.148
	895-2475		
	895-2475	182.159 uM	
		16.216	
		308.337	3.243
			0.649
			0.130
			60.23
			23.42
			-31.44
			132.78
			75.39
			39.30
			16.19
			33.65
			29.75
			148.84
			73.77
			28.14
			-20.74
			128.69
			68.37
			43.27
			19.44
			265.41
			287.86
			227.34
			65.40
			28.98

80/146

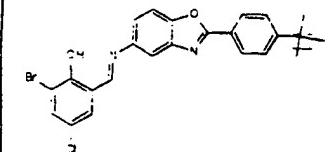
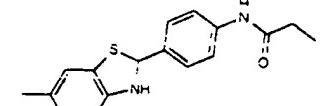
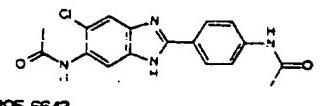
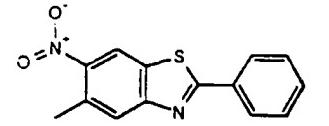
			
895-2544			
895-2544	189.186 uM		17.53
	18.919		136.50
264.284	3.784		59.15
	0.757		24.75
	0.151		11.86
			
895-3113			
895-3113	160.067 uM		-22.22
	16.007		224.52
312.372	3.201		68.48
	0.640		43.36
	0.128		30.56
			
895-3306			
895-3306	172.170 uM		-23.24
	17.217		38.63
290.41	3.443		333.10
	0.689		164.63
	0.138		64.33
			
895-3810			
895-3810	198.973 uM		89.79
	19.897		106.75
251.289	3.979		73.78
	0.798		33.45
	0.159		16.86

81 / 146

		
895-3846		
895-3846	193.267 uM	
	19.327	
	258.708	3.865
		0.773
		0.155
		
895-4642		
895-4642	176.473 uM	
	17.647	
	283.331	3.529
		0.706
		0.141
		
895-4843		
895-4843	159.581 uM	
	15.958	
	313.312	3.192
		0.638
		0.128
		
895-5185		
895-5185	182.433 uM	
	18.243	
	307.821	3.249
		0.650
		0.130

	-21.41	
	13.40	
	114.46	
	52.12	
	38.29	
	6.97	
	283.99	
	447.51	
	304.86	
	100.46	
	-17.18	
	24.54	
	100.12	
	60.37	
	27.85	
	-6.47	
	213.42	
	107.83	
	46.75	
	18.27	

82 / 146

		
895-5960		
895-5960	103.348 uM	
	10.335	
483.798	2.067	
	0.413	
	0.083	
		
895-6363		
895-6363	167.556 uM	
	16.755	
298.408	3.361	
	0.670	
	0.134	
		
895-6643		
895-6643	145.862 uM	
	14.586	
342.786	2.917	
	0.583	
	0.117	
		
895-7828		
895-7828	184.973 uM	
	18.497	
270.31	3.699	
	0.740	
	0.146	

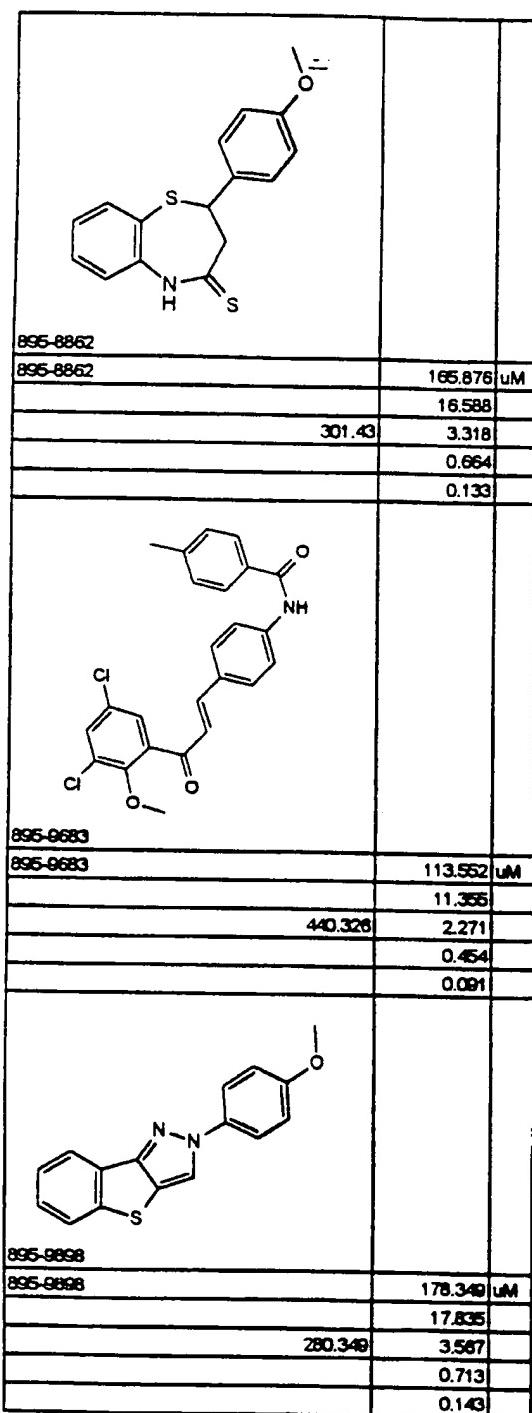
83 / 146

<chem>C1=CC2=C(NC2=CC(c3ccccc3)Nc4ccccc4)C1</chem>		
895-7985		
895-7985	223.935 uM	
	22.394	
	223.279	4.479
		0.898
		0.179
<chem>CC(=O)OCc1cc2c(s1)nc3ccccc3</chem>		
895-7997		
895-7997	176.461 uM	
	17.646	
	283.349	3.529
		0.708
		0.141
<chem>BrC1=NC2=C1C(=O)N=C2Cc3ccccc3</chem>		
895-8053		
895-8053	134.398 uM	
	13.440	
	372.03	2.668
		0.538
		0.108
<chem>CC1(C(O)C(O)C2[C@H](C[C@H]1O)[C@@H](O)C(=O)N2)O</chem>		
895-8137		
895-8137	169.326 uM	

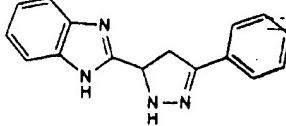
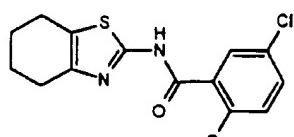
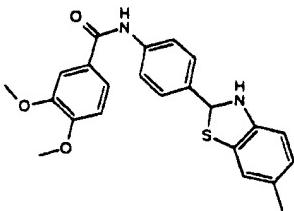
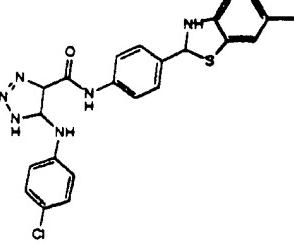
84/146

		16.933
	295.288	3.387
		0.677
		0.135
895-8185		
895-8185	219.057	uM
	21.906	
	228.251	4.381
		0.876
		0.175
895-8286		
895-8286	142.765	uM
	14.277	
	360.225	2.855
		0.571
		0.114
895-8383		
895-8383	191.774	uM
	19.177	
	260.724	3.835
		0.787
		0.153

85 / 146



86/146

		
896-0122		
896-0122	190.610	µM
	19.061	
262.316	3.812	
	0.762	
	0.152	
		
896-0246		
896-0246	154.888	µM
	15.489	
322.814	3.098	
	0.620	
	0.124	
		
896-0255		
896-0255	123.000	µM
	12.300	
408.504	2.460	
	0.492	
	0.098	
		
896-0346		
896-0346	107.532	µM
	10.753	

	-14.15	
	151.42	
	56.90	
	19.20	
	11.42	
	-17.57	
	34.35	
	102.03	
	48.52	
	20.52	
	-17.14	
	67.75	
	166.78	
	61.27	
	49.97	
	-18.88	
	77.80	

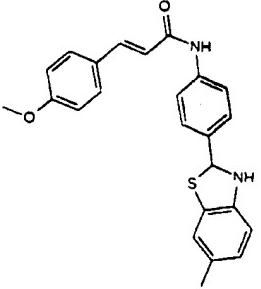
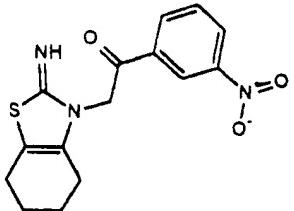
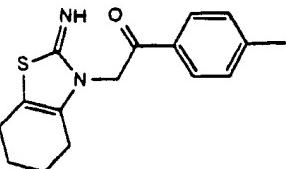
87/146

188.94
106.12
37.18
-16.90
87.23
210.25
73.35
28.25
-10.41
73.84
199.80
102.12
35.72
-16.32
105.46
115.43
53.88
27.03

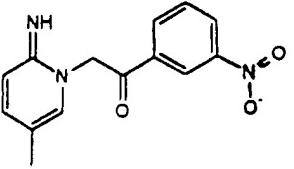
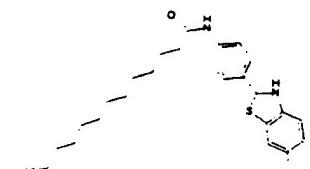
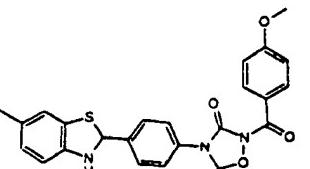
88/146

<chem>Clc1ccc(cc1)C(=O)Cc2ccnc(C)c2</chem>		
896-0686		
896-0686	191.774 uM	
	19.177	
260.724	3.835	
	0.767	
	0.153	
<chem>CC1=C(Cl)C=CC=C1N2C(=O)Cc3ccc(cc3)C2S1</chem>		
896-0692		
896-0692	131.269 uM	
	13.127	
360.697	2.625	
	0.525	
	0.105	
<chem>CC1=C(Cl)C=CC=C1N2C(=O)Cc3ccc(cc3)C2S1CCCCCCCCCCCC</chem>		
896-0719		
896-0719	91.950 uM	
	9.185	
543.774	1.839	
	0.368	
	0.074	
<chem>CC1=C(Cl)N(c2ccccc2)C(=O)c2cc(Cl)cc(Cl)cc2</chem>		
896-0773		
896-0773	147.228 uM	
	14.723	
339.609	2.945	
	0.589	
	0.116	

89 / 146

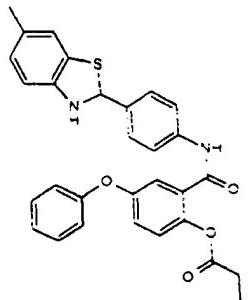
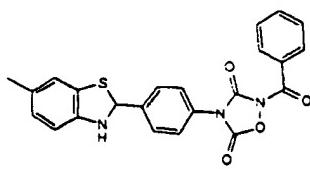
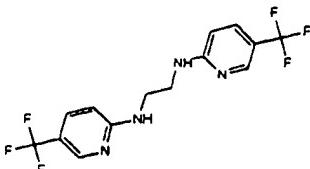
		
896-0819		
896-0819	124.219 uM	
	12.422	
402.516	2.484	
	0.497	
	0.099	
		
896-0853		
896-0853	157.546 uM	
	15.755	
317.367	3.151	
	0.630	
	0.126	
		
896-0921		
896-0921	174.583 uM	
	17.458	
286.397	3.492	
	0.886	
	0.140	

90/146

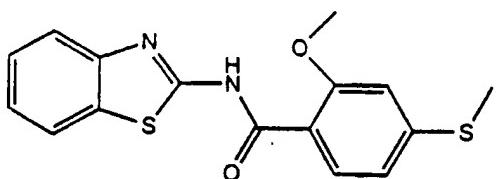
		
896-0836		
896-0836	184.314 uM	
	18.431	
271.276	3.686	
	0.737	
	0.147	
		
896-0859		
896-0859	103.798 uM	
	10.380	
481.703	2.076	
	0.415	
	0.083	
		
896-1201		
896-1201	108.343 uM	
	10.834	
481.496	2.167	
	0.433	
	0.087	

	-16.20
	153.61
	184.53
	79.16
	32.61
	-1.73
	102.48
	61.61
	63.58
	48.27
	-45.70
	92.57
	191.83
	47.22
	58.25

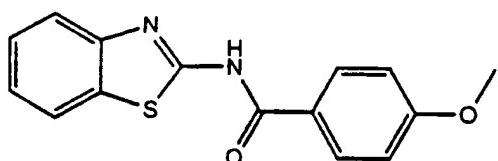
91 / 146

			
896-1301			
896-1301	97.922	μM	-24.32
	9.792		102.49
510.612	1.958		139.28
	0.392		97.89
	0.078		23.45
			
896-1349			
896-1349	115.883	μM	-39.92
	11.588		55.08
431.47	2.318		122.68
	0.464		67.25
	0.083		3.39
			
896-1362			
896-1362	142.749	μM	1.073.91
	14.275		1.082.17
360.268	2.855		884.71
	0.571		-9.82
	0.114		-20.37

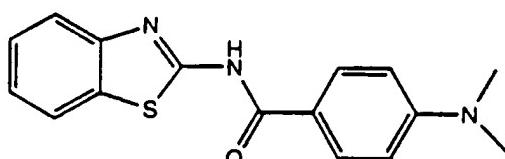
92 / 146



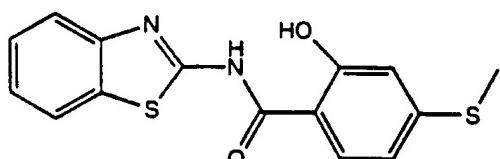
**Max : 215 %**  
**EC50 : < 0.8 nM**

**59-0072**

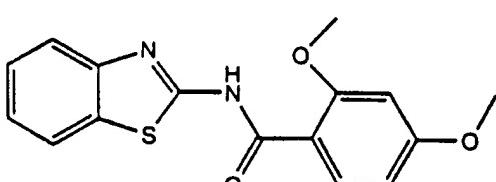
**Max : 121 %**  
**EC50 : 30 nM**

**59-0102**

**Max : 214 %**  
**EC50 : 200 nM**

**59-0070**

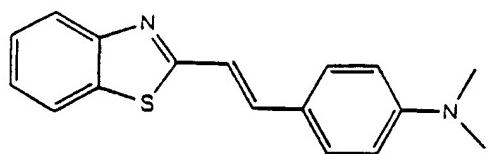
**Max : 54 %**  
**EC50 : 2 μM**

**59-0144**

**Max : 340 %**  
**EC50 : < 0.8 nM**

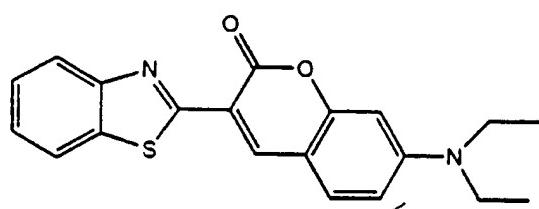
**59-0147****FIG. 5A**

93 /146

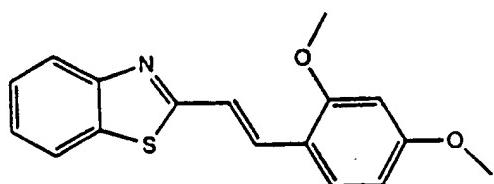


Max : 285 %  
EC50 : 3 nM

59-0099



Max : 269 %  
EC50 : < 0.8 nM

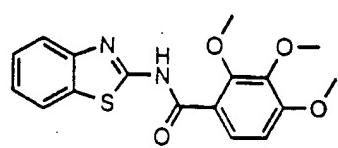


Max : 200 %  
EC50 : 30 nM

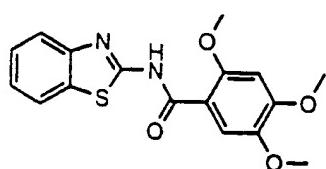
59-0210

5B  
FIG.

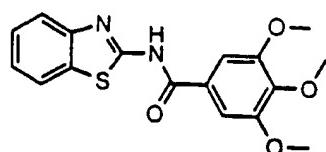
94 / 146



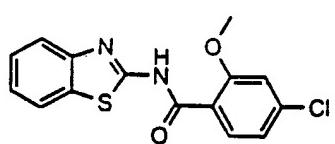
**59-0192**  
Max : 155 %  
EC50 : 20 nM



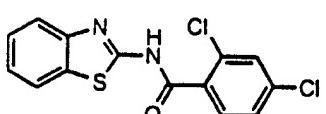
**59-0193**  
Max : 95 %  
EC50 : 30 nM



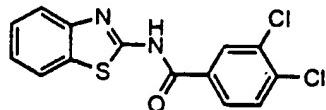
**59-0194**  
Inactive



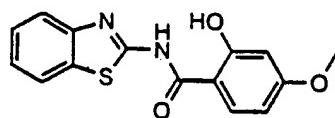
**59-0195**  
Max : 155 %  
EC50 : 20 nM



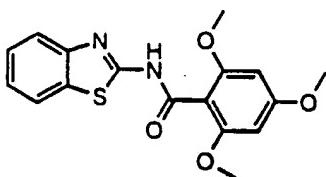
**59-0196**  
Inactive



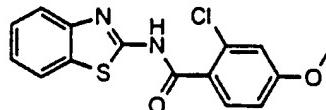
**59-0197**  
Max : 162 %  
EC50 : 150 nM



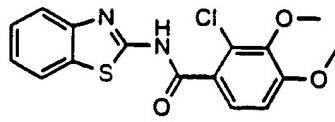
**59-0202**  
Max : 155 %  
EC50 : 150 nM



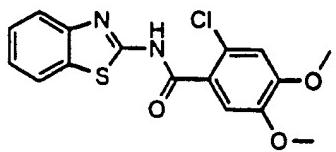
**59-0204**  
Max : 70 %  
EC50 : 50 nM



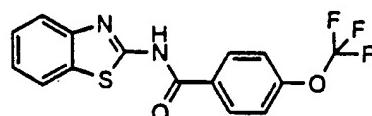
**59-0205**  
Max : 250 %  
EC50 : < 0.8 nM



**59-0206**  
Max : 150 %  
EC50 : 20 nM



**59-0207**  
Max : 50 %  
EC50 : 100 nM

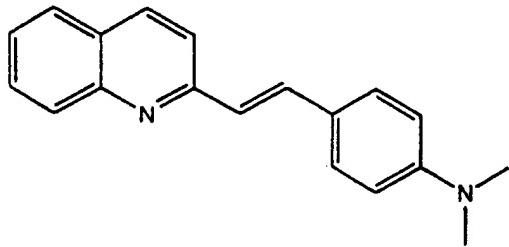


**59-0208**  
Max : 85 %  
EC50 : 1 uM

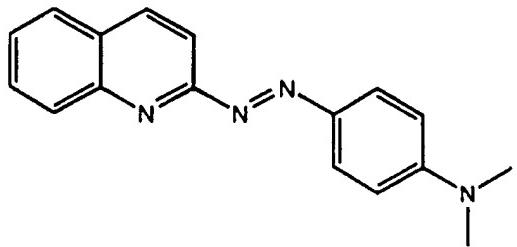
5C

FIG.

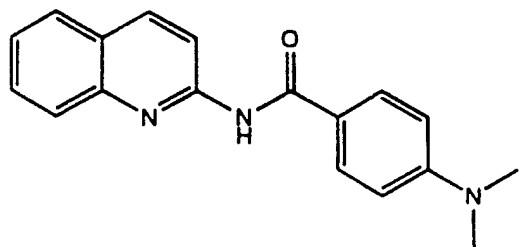
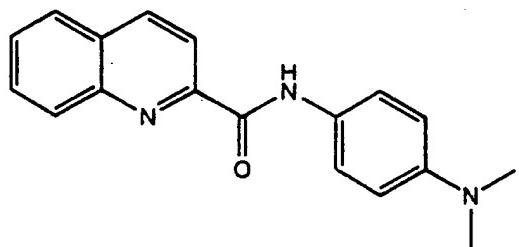
95/146



**50-0197**  
Max : 245 %  
EC50 : 3 nM

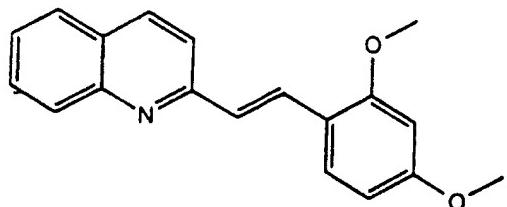


**59-0078**  
Max : 380 %  
EC50 : 1 nM

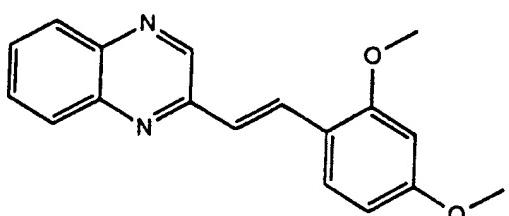


**FIG. 6A**

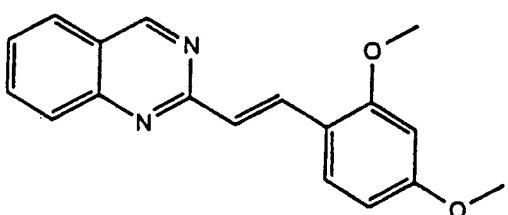
96 / 146



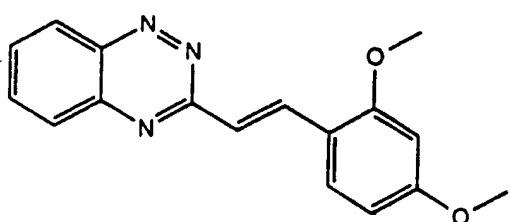
59-0199  
Max : 170 %  
EC50 : 100 nM



59-0203  
Max : 275 %  
EC50 : < 1 nM



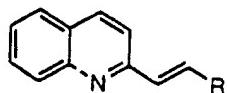
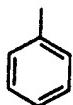
59-0286  
Max : 160 %  
EC50 : 300 nM



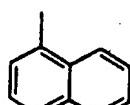
59-0285  
Max : 200 %  
EC50 : 30 nM

FIG. 6B

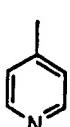
97 /146

 $R =$ 

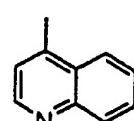
**59-0030**  
Max : 90 %  
EC50 : 1 uM



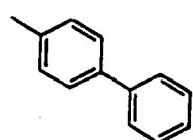
**59-0089**  
Max : 120 %  
EC50 : 5 uM



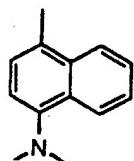
**59-0093**  
Max : 35 %  
EC50 : 5 uM



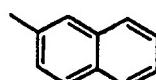
**59-0094**  
Max : 45 %  
EC50 : 10 uM



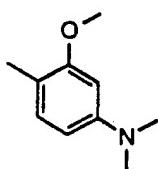
**59-0091**  
Max : 96 %  
EC50 : 1 uM



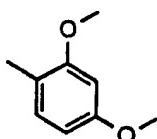
**59-0090**  
Max : 41 %  
EC50 : 10 uM



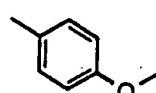
**59-0092**  
Max : 50 %  
EC50 : 10 uM



**59-0150**  
Max : 500 %  
EC50 : 1 nM



**59-0199**  
Max : 170 %  
EC50 : 100 nM

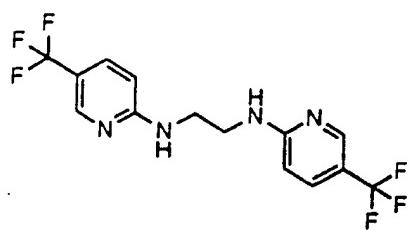


**59-0198**  
Max : 135 %  
EC50 : 100 nM

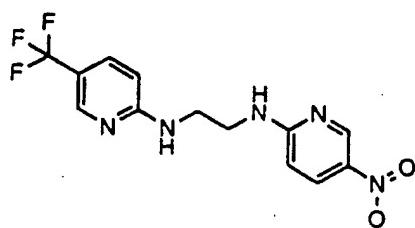
FIG.

6C

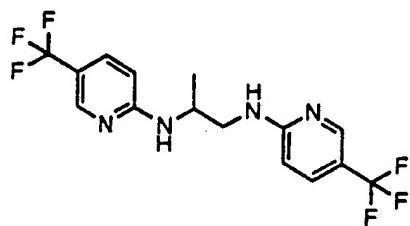
98 /146



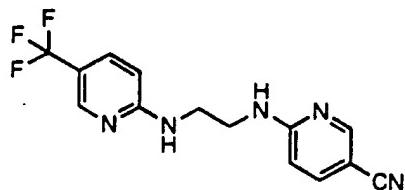
Max : 300 %  
EC50 : 0.5 uM



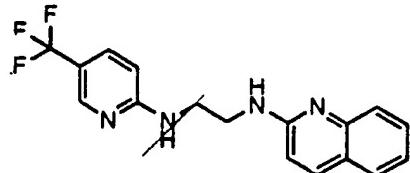
Max : 270 %  
EC50 : 5 uM



Max : 180 %  
EC50 : 5 uM



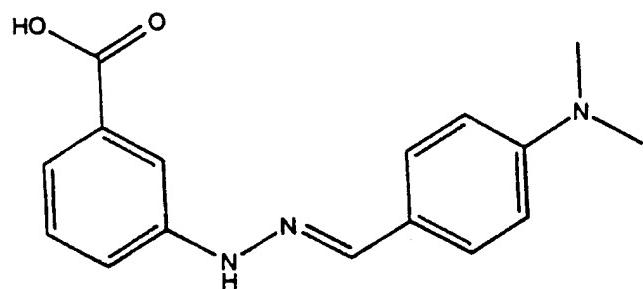
Max : 260 %  
EC50 : 3 uM



Max : 180 %  
EC50 : 5 uM

7  
FIG.

99 /146

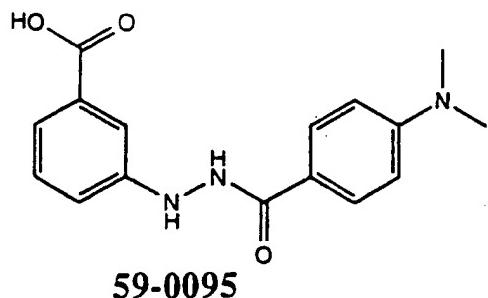


59-0045

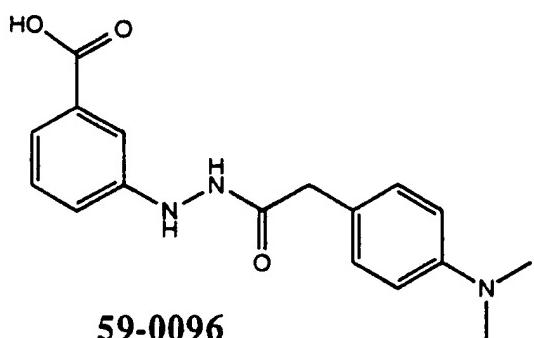
 $E_{CSO} = 5 \text{ nM}$ 

FIG. 8A

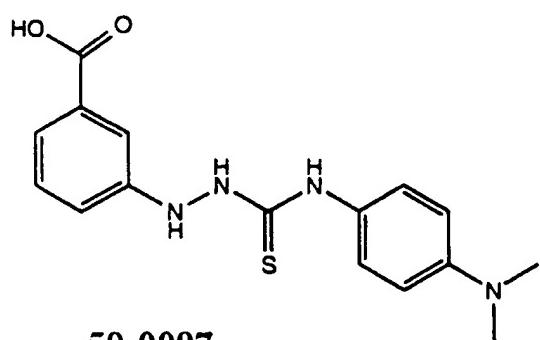
100 / 146



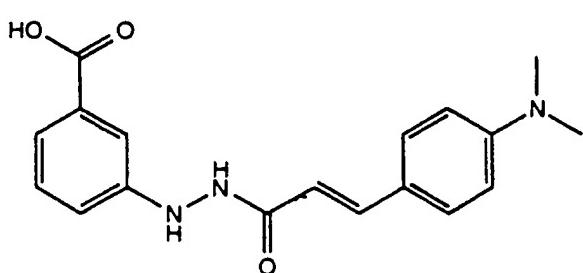
**Max : 48 %**  
**EC50 : 30  $\mu$ M**



**Max : 413 %**  
**EC50 : 93 nM**



**Max : 202 %**  
**EC50 : 100 nM**

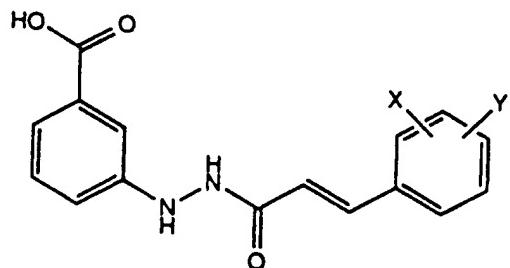


**Max : 222 %**  
**EC50 : 20 nM**

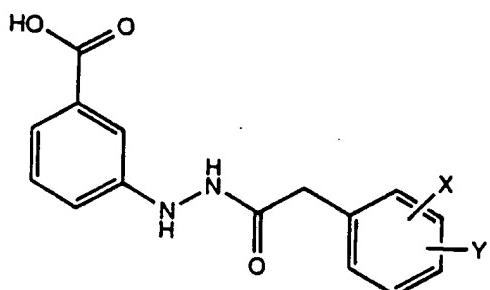
**FIG.**

86

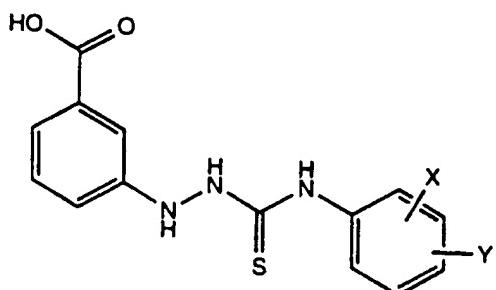
101 /146

 $X, Y = F, Cl, OMe$ 

&lt; 50 % max @ 100 uM

**59-0098 Analogs** $X, Y = F, Cl, OMe$ 

&lt; 50 % max @ 100 uM

**59-0096 Analogs** $X, Y = F, Cl, OMe$ 

&lt; 50 % max @ 100 uM

**59-0097 Analogs**8C  
FIG.

102 / 146

Compound	Compound Class	EC50	Max Response of 59-0008	Score	
				ZGI Score in Ex Vivo Assay	OS Screen in Ex Vivo Assay
59-0364	P	0	0	1	
59-0076	P	0	0	1	
59-0451	P	0	0	1	
59-0472	P	0	0	1	
59-0073	P	0	0		1+
59-0095	H	??	0.5x (30 uM)		1
59-0471	P	??	0.5x (100 uM)	1	
59-0030	Q	??	.7x (1uM)	1	1,1+
59-0470	P	50 uM	1.2x (100 uM)	1	
59-0450	P	5 uM	2.7x (30 uM)		
59-0459	P	5 uM	2x (10 uM)	1	
59-0064	Q	3 uM	1.5x (? uM)	1	

59-0008	Q	1 uM			1
59-0451	Q	300 nM	2x (30 uM)		1,2-
59-0106	T	300 nM	2x (9 uM)		1
59-0070	T	200nM	2x (3 uM)		1,1+
59-0097	H	100 nM?	2x (30 uM)		1+
59-0096	H	100 nM?	4x (100 uM)		1
59-0116	H	30 nM	2.5x (3 uM)		1+,2-
59-0210	T	30 nM	2x (3 uM)		1
59-0098	Q	20 nM	2x (9 uM)		1,2-
59-0019	Q	10 nM	2.5x (300 nM)	1+,2-	1,1+
59-0078	Q	9 nM	4x (1 uM)		1
59-0045	H	5 nM	4x (1uM)	1	1
50-0197	Q	3 nM	2.5x (300 nM)	1	1+,2-
59-0099	T	2 nM?	3x (1 uM)		1,1+
59-0282	Q	1 nM	2x (3 uM)		1+,2-
59-0203	Q	<1 nM	2x (30 uM)		1,2-
59-0072	T	300 pM	2x (uM)	1-1+	1,1+
59-0150	Q	<1 nM	5x (3 uM)	1-2?	1
59-0104	T	<1 nM	2x (uM)	1+,2-	1
59-0103	T	<1 nM	2x (30 nM)		1,1+
59-0124	T	<1 nM	2.5x (1 uM)		1+,2-
59-0205	T	<1 nM	2x (2 nM)		1

H = Hydrazone/Hydrazide (45) T = Benzothiazole (104)

Q = Quinoline/Quinoxaline (197)

P = Bis-pyridines (145)

Figure 9

103 /146

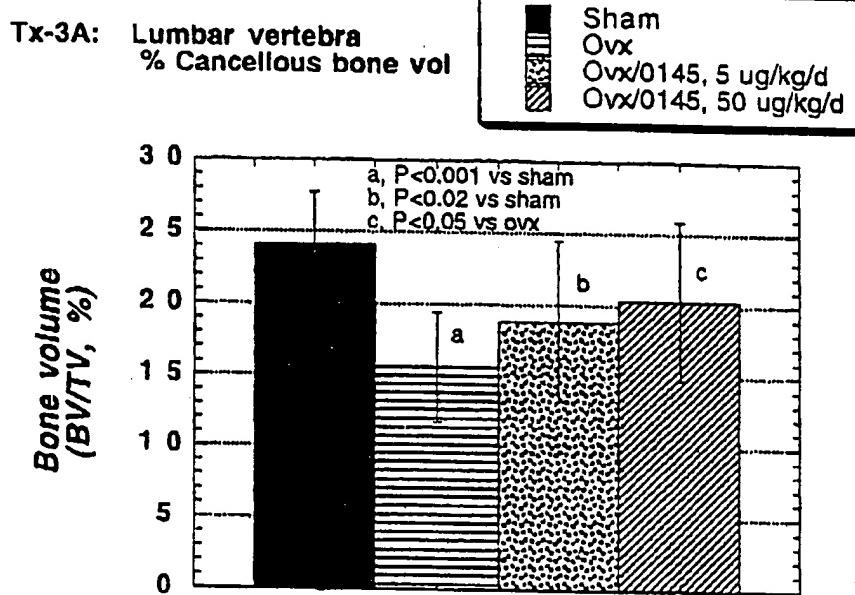
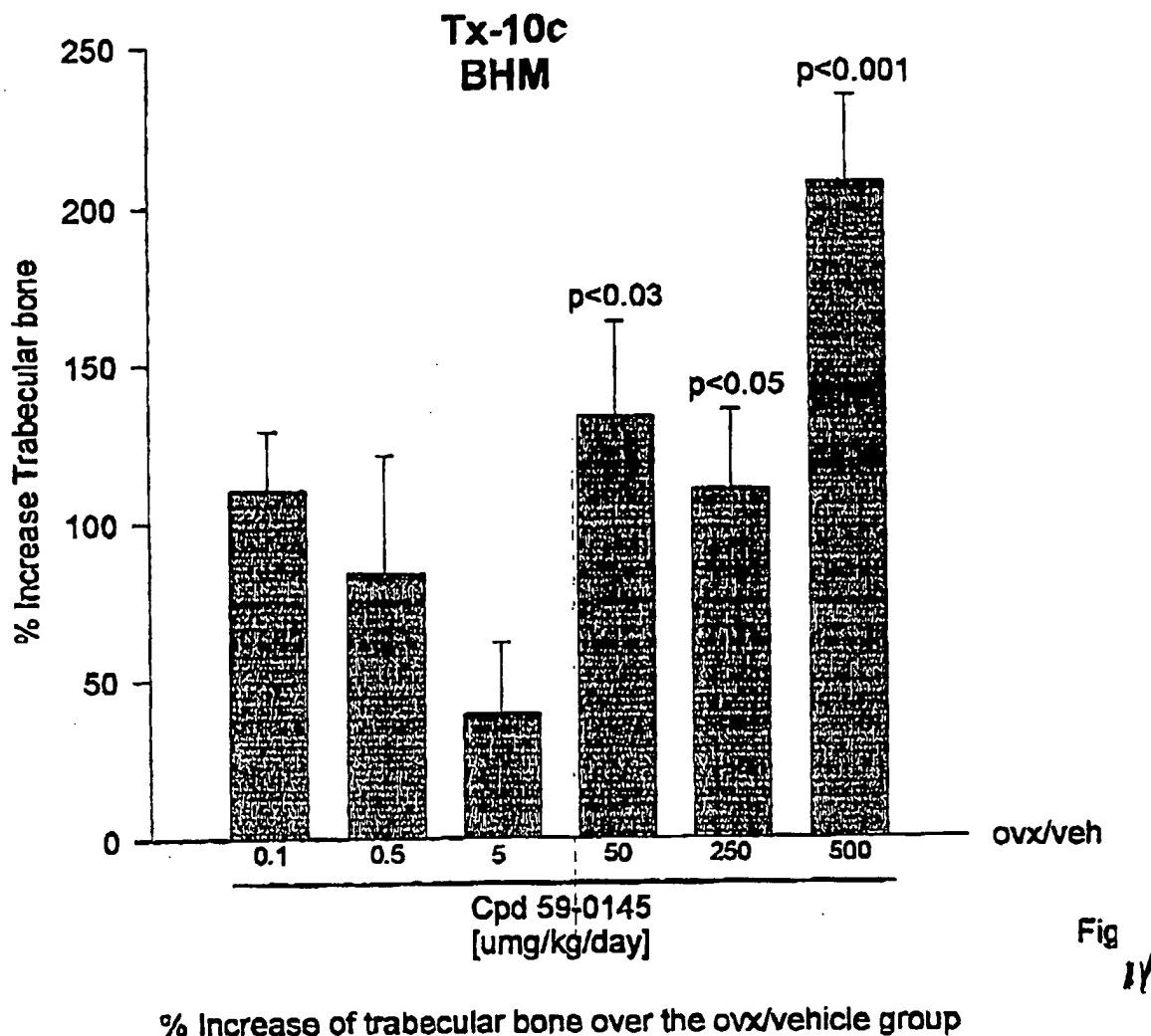


Fig 10

104 / 146



105 / 146

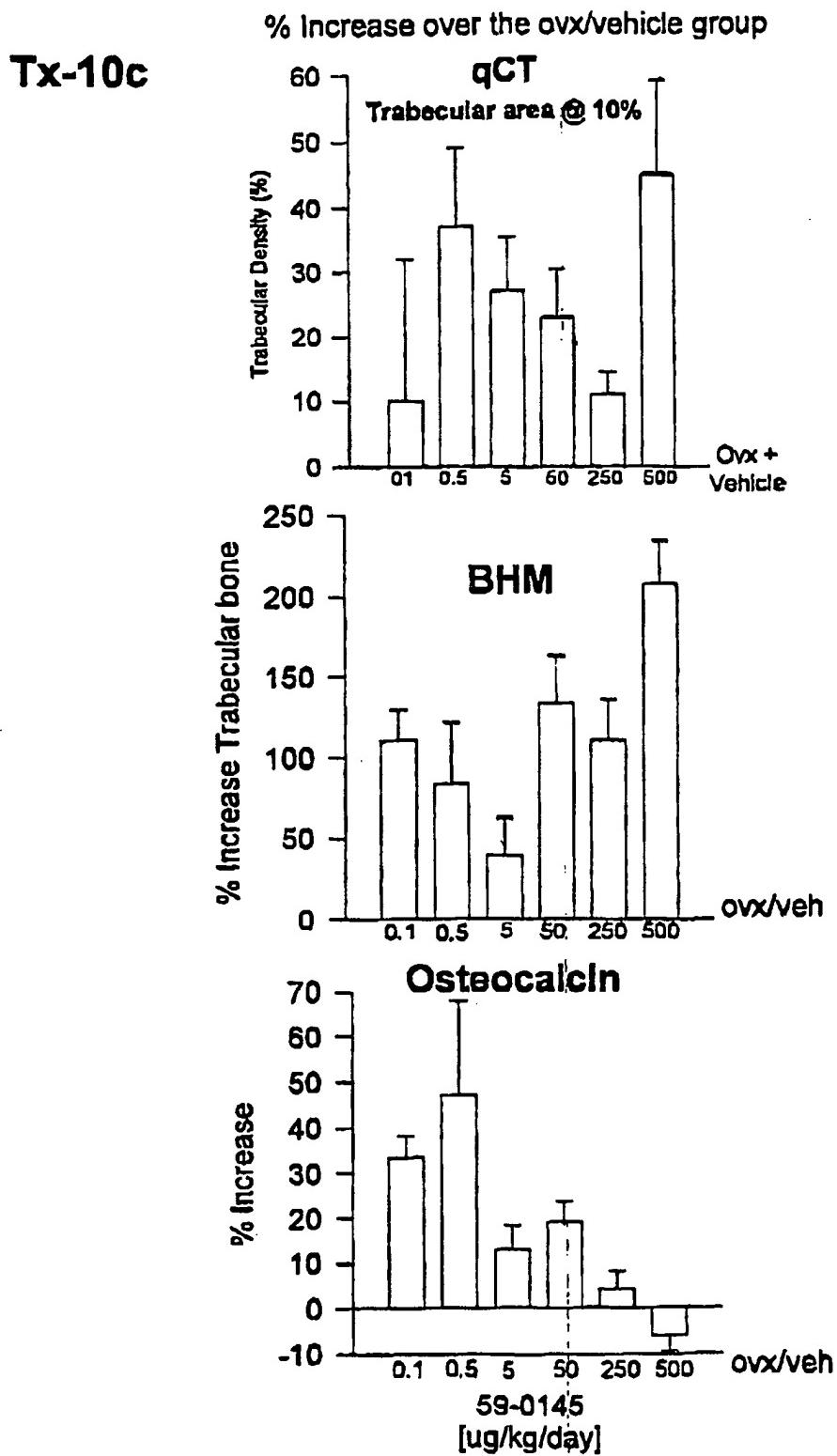
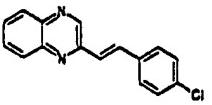
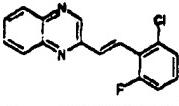
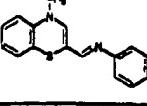
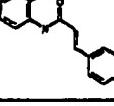
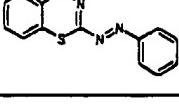
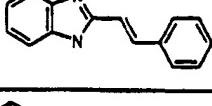
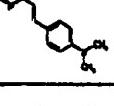
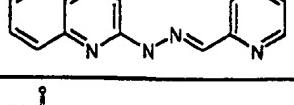
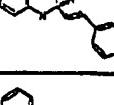
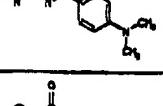
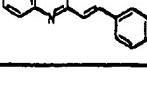


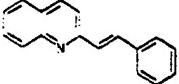
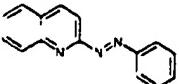
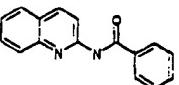
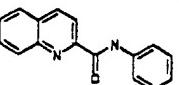
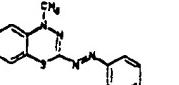
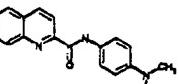
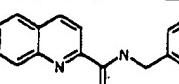
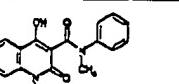
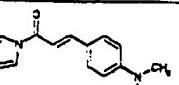
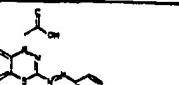
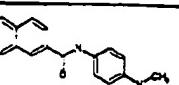
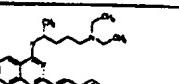
Fig 12

nand2

MOLSTRUCTURE	MOL>NNC	MOL WEIGHT NUM1
	59-0020	266.732
	59-0021	284.723
	59-0022	266.367
	59-0023	239.276
	59-0008	254.315
	59-0024	220.276
	59-0025	224.308
	59-0026	248.29
	59-0027	250.303
	59-0028	226.283
	59-0029	249.272

107 / 146

nand2

	59-0031	231.3	
	59-0030	233.275	
	59-0032	248.287	
	59-0033	248.287	
	59-0034	268.343	
	59-0035	291.356	
	59-0036	262.314	
	59-0037	308	
	59-0038	241.295	
	59-0039	312.352	
	59-0040	290.368	
	59-0041	501.902	

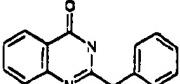
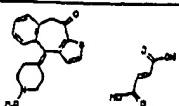
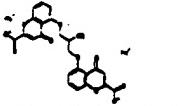
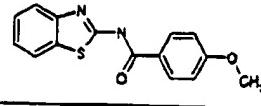
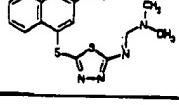
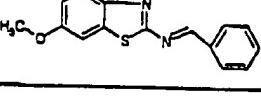
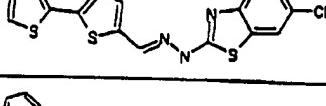
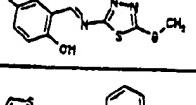
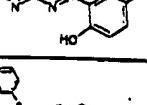
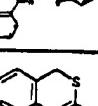
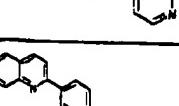
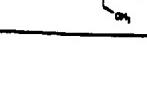
108 / 146

nand2

	59-0042	281.361
	59-0043	280.288
	59-0044	341.21
	59-0045	283.333
	59-0046	389.372
	59-0047	303.367
	59-0048	384.501
	59-0049	251.29
	59-0050	303.364
	59-0051	251.353
	59-0052	393.276
	59-0053	354.412

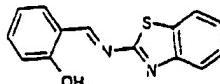
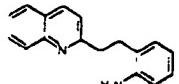
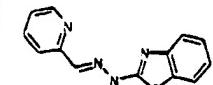
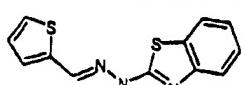
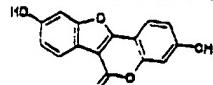
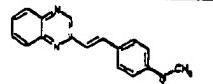
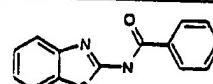
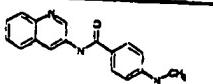
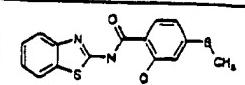
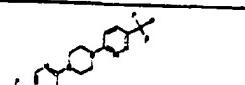
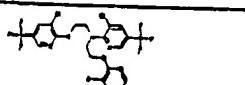
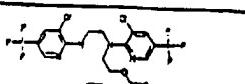
109 / 146

nand2

	59-0054	236.276
	59-0055	425.508
	59-0056	512.341
	59-0102	284.339
	59-0057	329.448
	59-0058	288.34
	59-0059	375.923
	59-0060	301.391
	59-0061	255.3
	59-0062	357.44
	59-0063	255.344
	59-0064	276.385

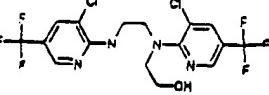
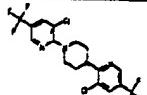
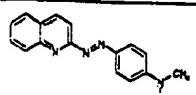
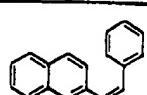
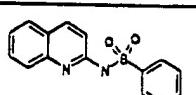
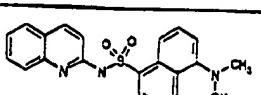
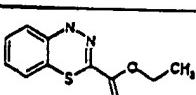
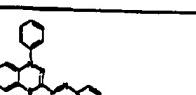
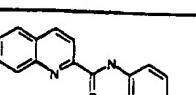
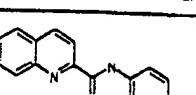
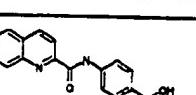
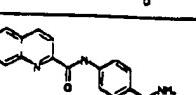
110 / 146

nand2

	59-0065	254.313	
	59-0066	248.33	
	59-0067	254.315	
	59-0068	259.354	
	59-0069	268.223	
	59-0070	275.353	
	59-0071	297.38	
	59-0072	291.352	
	59-0073	330.431	
	59-0074	376.303	
	59-0075	642.735	
	59-0075	618.775	

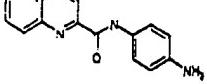
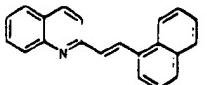
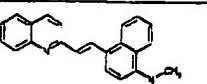
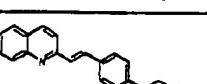
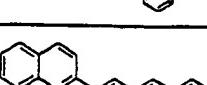
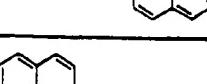
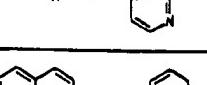
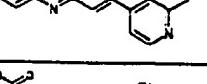
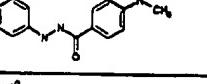
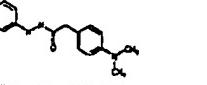
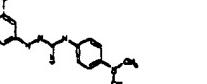
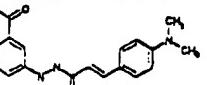
111 / 146

nand2

	59-0076	463.208
	59-0077	445.193
	59-0078	276.341
	59-0079	231.297
	59-0080	284.338
	59-0081	377.466
	59-0082	222.267
	59-0083	330.414
	59-0084	264.283
	59-0085	278.31
	59-0086	292.293
	59-0087	291.309

112 / 146

nand2

	59-0088	263.299	
	59-0089	281.357	
	59-0090	324.425	
	59-0091	307.394	
	59-0092	281.357	
	59-0093	232.285	
	59-0094	282.345	
	59-0095	299.328	
	59-0096	313.355	
	59-0097	330.41	
	59-0098	325.368	
	59-0099	280.393	

113 / 146

nand2

<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3ccccc3</chem>	59-0100	254.719
<chem>CN1CC=CC=C1Cc2ccc(cc2)C(F)(F)F</chem>	59-0101	230.232
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)Sc4ccccc4</chem>	59-0103	313.379
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC4CCOC4</chem>	59-0104	297.312
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC</chem>	59-0105	267.287
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC(=O)C</chem>	59-0106	297.312
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC(=O)COC</chem>	59-0107	332.378
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC(=O)COC(=O)C</chem>	59-0108	316.311
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC(=O)COC(=O)COC</chem>	59-0109	316.311
<chem>CN1C=CC=C1Cc2ccc(cc2)C(=O)c3cc(cc3)OC(=O)COC(=O)COC</chem>	59-0110	286.286
<chem>N#Cc1ccc(cc1)C(=O)O</chem>	59-0111	152.152
<chem>CN(C)c1ccc(cc1)C=O</chem>	59-0112	149.192

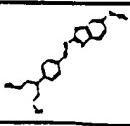
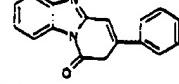
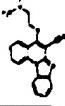
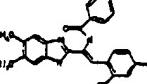
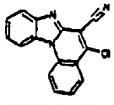
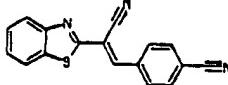
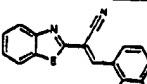
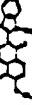
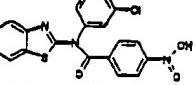
114 / 146

nand2

	59-0113	274.365
	59-0114	475.548
	59-0115	318.87
	59-0116	269.302
	59-0117	268.382
	59-0118	313.354
	59-0119	314.335
	59-0120	504.485
	59-0121	245.284
	59-0122	333.389
	59-0123	347.416
	59-0124	350.44

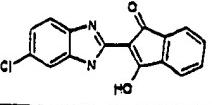
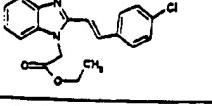
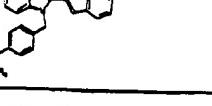
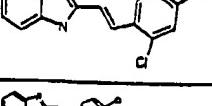
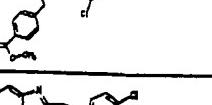
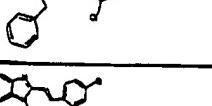
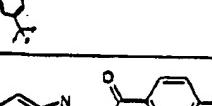
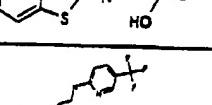
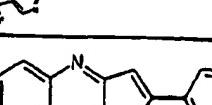
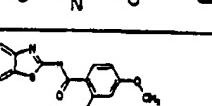
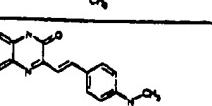
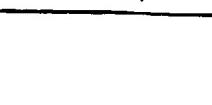
115 / 146

nand2

	59-0125	372.447
	59-0126	260.295
	59-0127	329.405
	59-0128	436.34
	59-0129	277.713
	59-0130	287.345
	59-0131	331.225
	59-0132	313.315
	59-0133	327.342
	59-0134	357.367
	59-0135	356.383
	59-0136	411.868

116 / 146

nand2

	59-0137	296.712
	59-0138	340.808
	59-0139	340.424
	59-0140	289.164
	59-0141	437.324
	59-0142	379.288
	59-0143	447.285
	59-0144	316.404
	59-0145	350.265
	59-0146	246.268
	59-0147	314.364
	59-0148	291.352

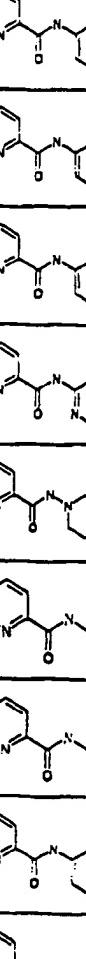
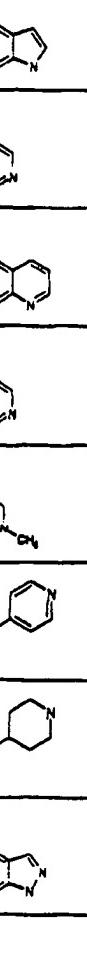
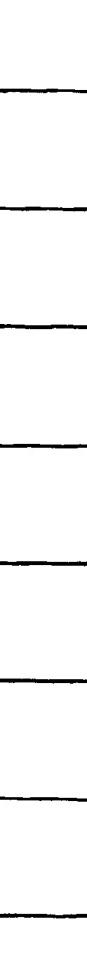
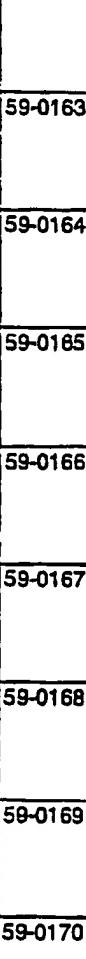
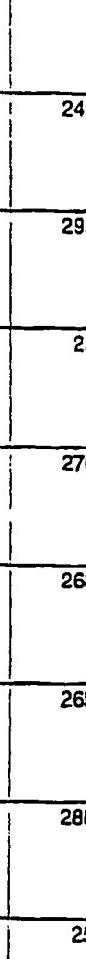
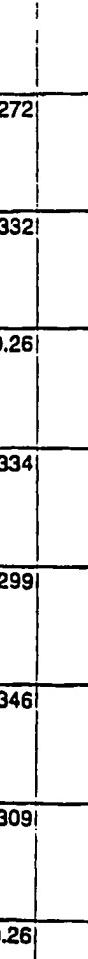
117 / 146

nand2

<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(O)c4c3[nH]c4)C(=O)[O-]</chem>	59-0149	329.335	
<chem>CN1C=CC=C1c2ccccc2Cc3ccc(O)c4c3[nH]c4</chem>	59-0150	304.391	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(O)c4c3[nH]c4)C(F)F</chem>	59-0151	278.31	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(F)cc4c3[nH]c4)C(F)F</chem>	59-0152	266.274	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(Cl)cc4c3[nH]c4)C(F)F</chem>	59-0153	282.729	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C)cc4c3[nH]c4)C(F)F</chem>	59-0154	262.311	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)F)cc4c3[nH]c4)C(F)F</chem>	59-0155	316.281	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)c4ccccc4)cc4c3[nH]c4)C(F)F</chem>	59-0156	333.389	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)c4ccccc4)cc4c3[nH]c4)C(F)F</chem>	59-0157	290.364	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)c4ccccc4)cc4c3[nH]c4)C(F)F</chem>	59-0158	308.335	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)c4ccccc4)cc4c3[nH]c4)C(F)F</chem>	59-0159	308.335	
<chem>CN1C=CC=C1c2ccccc2C(=O)N(c3ccc(C(F)(F)c4ccccc4)cc4c3[nH]c4)C(F)F</chem>	59-0160	319.406	

118 / 146

nand2

	59-0161	291.352
	59-0162	287.321
	59-0163	249.272
	59-0164	299.332
	59-0165	250.26
	59-0166	270.334
	59-0167	263.299
	59-0168	269.346
	59-0169	288.309
	59-0170	250.26
	59-0171	238.249
	59-0172	306.32

119 / 146

nand2

	59-0173	299.332	
	59-0174	279.298	
	59-0175	306.348	
	59-0176	256.288	
	59-0177	251.248	
	59-0178	239.267	
	59-0179	257.292	
	59-0180	417.487	
	59-0181	313.358	
	59-0182	288.309	
	59-0183	305.36	
	59-0184	252.272	

120 / 146

nand2

	59-0185	345.444	
	59-0186	374.382	
	59-0187	389.494	
	59-0188	616.784	
	59-0189	490.579	
	59-0190	550.631	
	59-0191	584.605	
	59-0192	344.389	
	59-0193	344.389	
	59-0194	344.389	
	59-0195	318.783	
	59-0196	323.202	

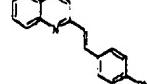
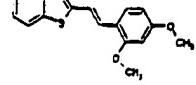
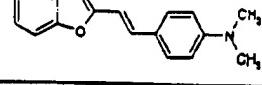
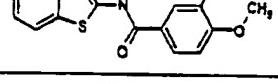
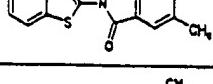
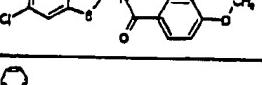
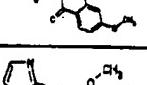
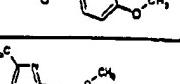
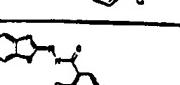
121 / 146

nand2

<chem>CN1C=CC=C1c2ccccc2C(=O)c3ccc(Cl)cc3</chem>	59-0197	323.202	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2</chem>	59-0198	261.323	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2</chem>	59-0199	291.348	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2Cc3ccc(OCC)cc3</chem>	59-0200	342.349	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2Cc3ccc(OCC)cc3</chem>	59-0201	331.326	
<chem>CN1C=CC=C1C(O)c2ccc(OCC)cc2C(=O)c3ccc(Cl)cc3</chem>	59-0202	300.337	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2</chem>	59-0203	292.336	
<chem>CN1C=CC=C1Cc2ccc(OCC)cc2Cc3ccc(OCC)cc3</chem>	59-0204	344.389	
<chem>CN1C=CC=C1C(O)c2ccc(OCC)cc2C(=O)c3ccc(Cl)cc3</chem>	59-0205	318.783	
<chem>CN1C=CC=C1C(O)c2ccc(OCC)cc2C3=C(Cl)C=C(C=C3)C(=O)c4ccc(Cl)cc4</chem>	59-0206	348.809	
<chem>CN1C=CC=C1C(O)c2ccc(OCC)cc2C3=C(Cl)C=C(C=C3)C(=O)c4ccc(Cl)cc4</chem>	59-0207	348.809	
<chem>CN1C=CC=C1C(O)c2ccc(OCC)cc2C(F)(F)C(F)(F)C(F)(F)C(F)(F)</chem>	59-0208	338.308	

122 / 146

nand2

	59-0209	247.296	
	59-0210	297.376	
	59-0211	264.326	
	59-0212	314.364	
	59-0213	294.333	
	59-0214	348.809	
	59-0215	340.401	
	59-0216	264.304	
	59-0217	278.331	
	59-0218	292.357	
	59-0219	329.379	
	59-0220	300.312	

123 / 146

nand2

<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0221	283.329	
<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0222	309.367	
<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)C(=O)O</chem>	59-0223	284.27	
<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)c3cc(O)cc4c(c3)C(=O)OC(=O)c4</chem>	59-0224	330.338	
<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)C(=O)O</chem>	59-0225	256.26	
<chem>O=Cc1ccc(cc1)N=Nc2ccc(cc2)C(=O)[O-]</chem>	59-0226	285.258	
<chem>C1CCC2C(C1)CC3=C2C=CC=C3</chem>	59-0227	296.398	
<chem>CCOC(=O)c1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0228	269.946	
<chem>CCN(C)c1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0229	239.32	
<chem>O=[N+]([O-])c1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0230	284.317	
<chem>CS(=O)(=O)c1ccc(cc1)N=Nc2ccc(cc2)N(C)C</chem>	59-0231	318.399	
<chem>CN1C=NC2=C1C=CN(C)c3ccc(cc3)N2c4ccc(cc4)N(C)C</chem>	59-0232	269.35	

124 /146

nand2

<chem>C=CCc1ccccc1Nc2ccccc2</chem>	59-0233	232.285	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2</chem>	59-0234	281.31	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3</chem>	59-0235	251.284	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCC</chem>	59-0236	280.325	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC</chem>	59-0237	328.39	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4</chem>	59-0238	340.401	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)O</chem>	59-0239	330.338	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)OCC</chem>	59-0240	347.393	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)OCC(=O)O</chem>	59-0241	344.753	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)OCC(=O)OCC</chem>	59-0242	291.286	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)OCC(=O)OCC(=O)O</chem>	59-0243	455.934	
<chem>C=C[C@H](C)c1ccccc1Nc2ccccc2Cc3ccccc3OCCOC(=O)N4Cc5ccccc5N(c6ccccc6)C4C(=O)OCC(=O)OCC(=O)OCC</chem>	59-0244	414.935	

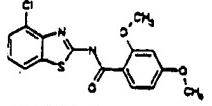
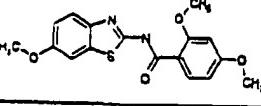
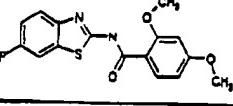
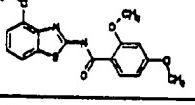
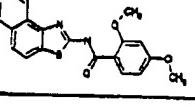
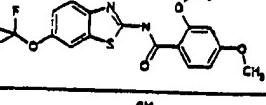
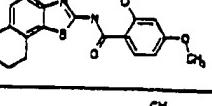
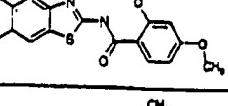
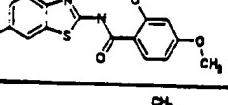
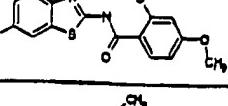
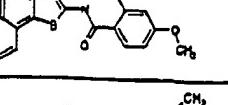
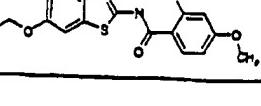
125 / 146

nand2

	59-0245	419.887	
	59-0246	675.856	
	59-0247	933.385	
	59-0248	247.296	
	59-0249	298.297	
	59-0250	332.742	
	59-0251	386.426	
	59-0252	361.376	
	59-0253	348.809	
	59-0254	328.39	
	59-0255	376.455	
	59-0256	361.376	

126 /146

nand2

	59-0257	348.809	
	59-0258	344.389	
	59-0259	332.354	
	59-0260	344.389	
	59-0261	364.423	
	59-0262	398.36	
	59-0263	368.455	
	59-0264	383.254	
	59-0265	393.26	
	59-0266	328.39	
	59-0267	364.423	
	59-0268	358.416	

127 / 146

nand2

<chem>CN1C=CC2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0269	342.417
<chem>CN1C=CC2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0270	328.39
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0271	360.364
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0272	381.838
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0273	345.445
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0274	329.379
<chem>CN1C=CC2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0275	328.39
<chem>CN1C=CC2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0276	358.373
<chem>CN1C=CC2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0279	327.406
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0277	372.375
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0278	372.375
<chem>CC1=CC=C2=C1SC(=O)N(C(=O)c3ccc(Oc4ccccc4)cc3)C2</chem>	59-0280	294.352

128 / 146

nand2

	59-0281	310.419	
	59-0282	305.379	
	59-0283	306.367	
	59-0284	305.379	
	59-0285	293.324	
	59-0286	292.336	
	59-0287	306.32	
	59-0288	276.357	
	59-0289	351.188	
	59-0290	351.188	
	59-0291	342.349	
	59-0292	372.375	

129 / 146

nand2

<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)c(O*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0293	342.349	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(F)cc(F)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0294	318.278	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)cc(*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0295	312.323	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)cc(*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0296	316.743	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)cc(*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0297	329.31	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)cc(O*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0298	298.297	
<chem>*C(=O)c1ccc(cc1)N(C(=O)Cc2cc(*)cc(*)cc2)C(=O)c3ccc(cc3)OC</chem>	59-0299	304.308	
<chem>*C(=O)c1ccc(cc1)C(=O)Cc2cc(*)cc(*)cc2</chem>	59-0300	236.269	
<chem>*C(=O)c1ccc(cc1)C(=O)Cc2cc(*)cc(*)cc2</chem>	59-0301	326.35	
<chem>*C(=O)c1ccc(cc1)N2C(*)C(*)c3cc(*)nc(*)c3N2</chem>	59-0302	285.733	
<chem>*C(=O)c1ccc(cc1)N2C(*)C(*)c3cc(*)nc(*)c3N2</chem>	59-0303	275.31	
<chem>*C(=O)c1ccc(cc1)N2C(*)C(*)c3cc(*)nc(*)c3N2</chem>	59-0304	469.178	

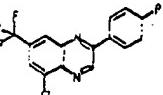
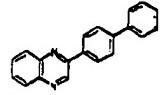
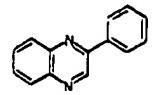
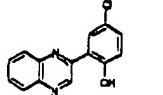
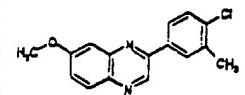
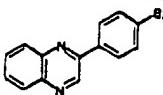
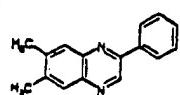
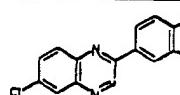
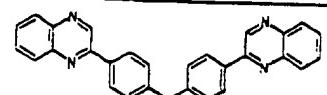
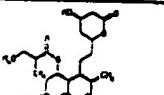
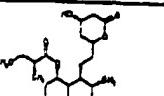
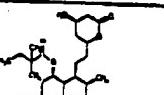
130 / 146

nand2

<chem>C1=CC=C(C=C1)N2C(=O)c3ccccc3S2(=O)(=O)c4ccccc4</chem>	59-0305	340.789
<chem>CC(=O)c1nc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0306	308.403
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0307	300.38
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0308	304.27
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0309	330.406
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0310	368.378
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0311	287.705
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0313	293.127
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0314	343.134
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0315	275.137
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0316	303.191
<chem>CC(=O)c1cc2c(cc1Cc3ccccc3)sc2Cc4ccccc4</chem>	59-0317	377.579

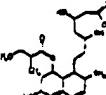
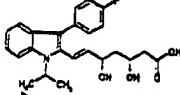
131 / 146

nand2

	59-0318	326.679
	59-0319	282.345
	59-0320	206.247
	59-0321	256.691
	59-0322	284.745
	59-0323	285.143
	59-0324	294.301
	59-0312	309.582
	59-0325	424.505
	59-0326	404.543
	59-0327	390.517
	59-0328	418.57

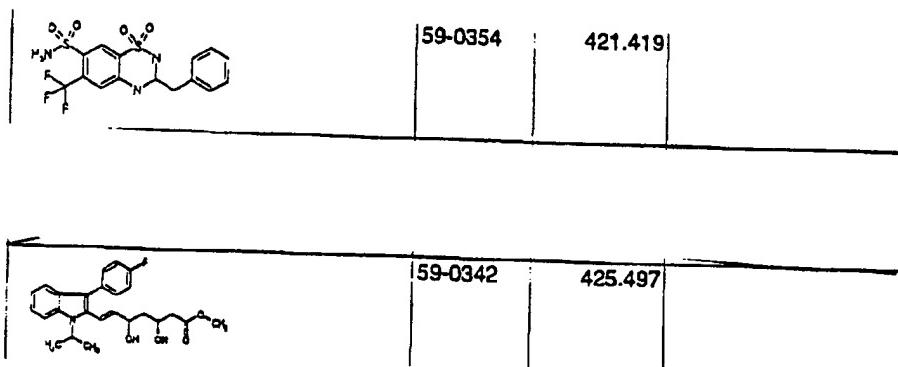
132 / 146

nand2

	59-0329	424.53
	59-0330	411.47

133 /146

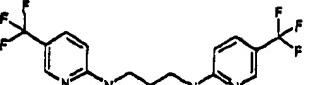
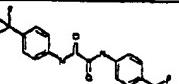
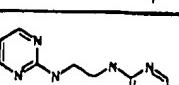
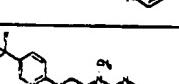
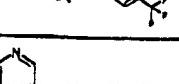
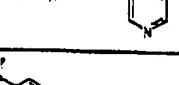
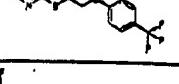
nand2



134 / 146

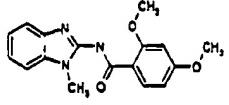
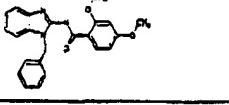
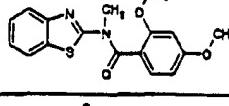
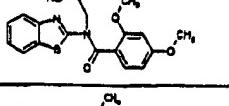
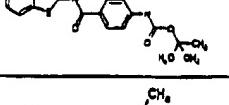
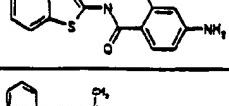
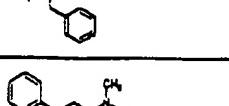
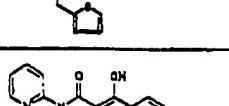
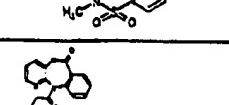
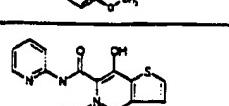
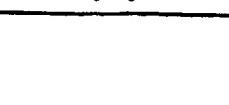
nand2



	59-0361	364.292	
	59-0362	376.255	
	59-0363	216.247	
	59-0364	378.318	
	59-0365	216.247	
	59-0366	384.367	
	59-0367	348.289	

135 / 146

nand2

	59-0368	311.3391
	59-0369	387.4371
	59-0370	328.39
	59-0371	372.3991
	59-0372	399.4691
	59-0373	299.3531
	59-0374	255.3631
	59-0375	261.3911
	59-0376	331.3511
	59-0377	351.4081
	59-0378	285.3891
	59-0379	397.3791

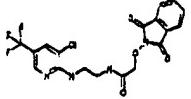
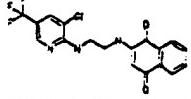
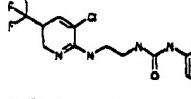
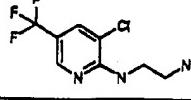
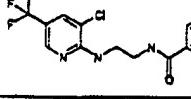
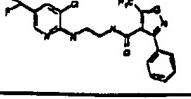
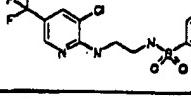
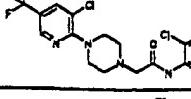
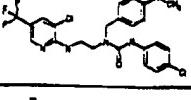
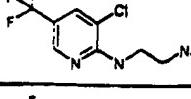
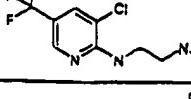
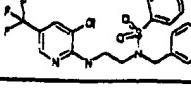
136 / 146

nand2

	59-0380	408.813
	59-0381	408.813
	59-0382	408.813
	59-0383	468.699
	59-0384	340.405
	59-0385	334.377
	59-0386	367.761
	59-0387	323.729
	59-0388	451.23
	59-0389	474.268
	59-0390	487.284
	59-0391	466.245

137 / 146

nand2

	59-0392	442.78
	59-0393	395.767
	59-0394	393.195
	59-0395	370.804
	59-0396	378.18
	59-0397	424.808
	59-0398	414.234
	59-0399	502.245
	59-0400	526.388
	59-0401	364.197
	59-0402	382.181
	59-0403	538.803

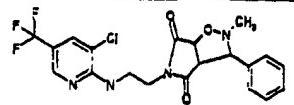
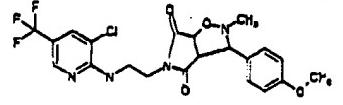
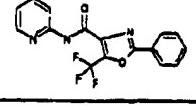
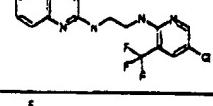
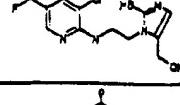
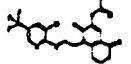
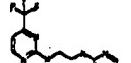
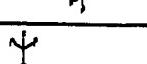
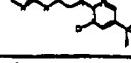
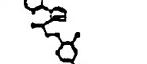
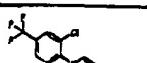
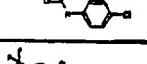
138 / 146

nand2

	59-0404	549.378
	59-0405	437.315
	59-0406	406.233
	59-0407	349.699
	59-0408	561.868
	59-0409	535.821
	59-0410	340.428
	59-0411	464.294
	59-0412	429.849
	59-0413	459.874
	59-0414	497.846
	59-0415	518.905

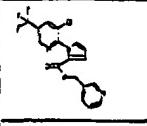
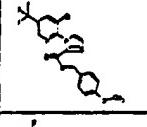
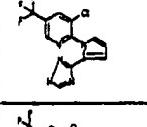
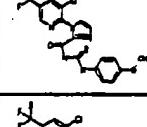
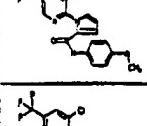
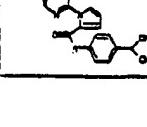
139 / 146

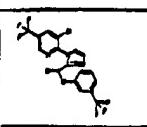
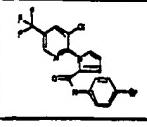
nand2

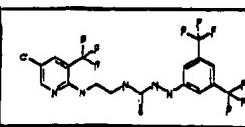
	59-0416	454.834	
	59-0417	484.86	
	59-0418	333.268	
	59-0419	367.761	
	59-0420	352.767	
	59-0421	539.339	
	59-0422	351.253	
	59-0423	385.698	
	59-0424	484.188	
	59-0425	400.186	
	59-0426	380.756	
	59-0427	414.213	

140 / 146

nand2

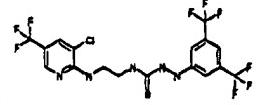
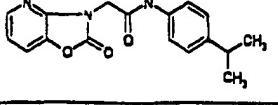
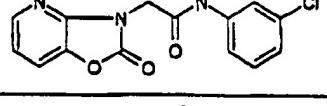
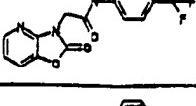
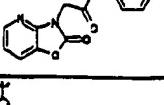
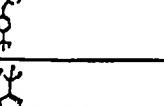
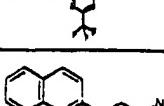
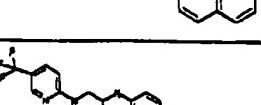
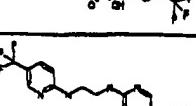
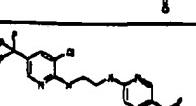
	59-0428	380.756
	59-0429	409.793
	59-0430	313.669
	59-0431	454.859
	59-0492	395.767
	59-0433	407.821

	59-0435	433.738
	59-0436	444.637

	59-0439	525.826
---	---------	---------

141 / 146

nand2

	59-0440	525.826
	59-0441	311.339
	59-0442	303.704
	59-0443	337.256
	59-0444	269.259
	59-0445	404.356
	59-0446	404.356
	59-0447	352.241
	59-0448	314.39
	59-0449	394.274
	59-0450	329.281
	59-0451	384.71

142 / 146

nand2

<chem>Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0452	242.324
<chem>Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0453	214.271
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0454	264.291
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0455	300.32
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0456	308.296
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0457	330.342
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0458	300.408
<chem>C#Cc1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N#C</chem>	59-0459	364.292
<chem>C(F)(F)c1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0460	252.238
<chem>C(F)(F)c1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0461	266.265
<chem>C(F)(F)c1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0462	280.292
<chem>C(F)(F)c1ccc(cc1)NCCN(c2ccc(O)cc2)c3ccc(cc3)N</chem>	59-0463	253.226

143 / 146

nand2

<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0464	267.253
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0465	363.26
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0466	315.352
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0467	212.294
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0468	213.289
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0469	378.318
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0470	325.293
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0471	350.261
<chem>CN(C)c1ccc(cc1)N(Cc2ccccc2)c3ccccc3</chem>	59-0472	351.249

144 / 146

nand2

<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0476	350.265
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0477	283.256
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0478	351.253
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0479	283.256
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0480	332.328
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0481	363.26
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0482	349.277
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0483	307.278
<chem>[Cl-]C1=CC=C(C=C1)N(Cc2ccccc2)[Cl-]</chem>	59-0484	315.246
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0485	250.3
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0486	364.292
<chem>*c1ccc(cc1)CCN(c2ccccc2)Cc3ccccc3</chem>	59-0487	302.298

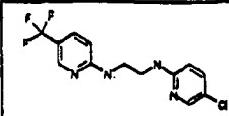
145 / 146

nand2

	59-0488	486.259
	59-0489	255.3
	59-0490	322.309
	59-0491	317.269
	59-0492	289.161
	59-0493	364.248
	59-0494	232.285
	59-0495	299.294
	59-0496	354.33
	59-0497	340.303
	59-0498	282.268
	59-0499	296.294

146 / 146

nand2

	59-0500	316.713

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/18864

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-structure

APS-diaryl, bone, osteo?, BMP

DIALOG-diaryl, bone, osteo?, BMP

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,964 A (BRYANT et al.) 15 August 1995, see entire document.	1-2, 5-28, 55-56
Y	US 5,523,309 A (BRYANT et al.) 04 June 1996, see entire document, especially claim 8.	1-2, 5-28, 55-56
Y,P	US 5,622,974 A (MUEHL) 22 April 1997, see entire document, especially claim 5.	1-2, 5-28, 55-56
Y	WO 93/10113 A1 (TEIKOKU HORMONE MFG. CO., LTD.) 27 May 1993, see entire document.	1-2, 5-28, 55-56
Y	WO 95/10513 A1 (PFIZER INC.) 20 April 1995, see entire document, especially claim 20.	1-2, 5-30, 55-56
Y	US 5,280,040 A (LABROO et al.) 18 January 1994, see entire document.	1-4, 31-43, 55-56

<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
-------------------------------------	--	--------------------------	--------------------------

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance		
"B" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search  28 JANUARY 1998	Date of mailing of the international search report  26 FEB 1998
--	---

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  CELIA CHANG Telephone No. (703) 308-1235
---	---

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US97/18864
---

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
Y	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmacol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Y	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridybut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A study using triarylbutenone, benzofuran and triarylfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	1-2, 50-56
Y	VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol. 761, pages 176-191, see especially pages 178-180.	1-2, 5-28, 55-56

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/US97/18864**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/US97/18864**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (6): A61K 31/165, 31/215; 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL : 514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

**B. FIELDS SEARCHED**

Minimum documentation searched

Classification System: U.S.

514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The claims are deemed to correspond to the species as listed in the following manner:

Group I, claims 3-4 and 31-43 compounds corresponding to Ar1 is condensed six membered heterocyclic ring, Ar2 is various aromatic rings;

Group II, claims 5-28, compounds corresponding to Ar1 is condensed five membered heterocyclic ring, Ar2 is various aromatic rings;

Group III, claims 29-30, compounds corresponding to Ar1 is isolated five membered heterocyclic ring, Ar2 is various aromatic rings;

Group IV, claims 44-49, compounds corresponding to Ar1 is isolated six membered heterocyclic ring, Ar2 is various aromatic rings;

Group V, claims 50-54, compounds corresponding to Ar1 is phenyl ring, Ar2 is various aromatic rings;

Group VI, claims 1-2, 55-56 in part (remaining compounds)

The following claims are generic: 1-2, 55-56

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2 and ANNEX B section (f), the species lack the same or corresponding special technical features for the following reasons:

The six groups of compounds corresponding to method of treating conditions of deficiency in bone growth, resorption or replacement using structurally distinctive compounds. Each group of compounds as delineated above does not share significant structural element (see Ar1, Ar2 and L are all variables, thus, not common element). In addition, at least one Markush alternative is found in CA 127:17703.